

Figure 1

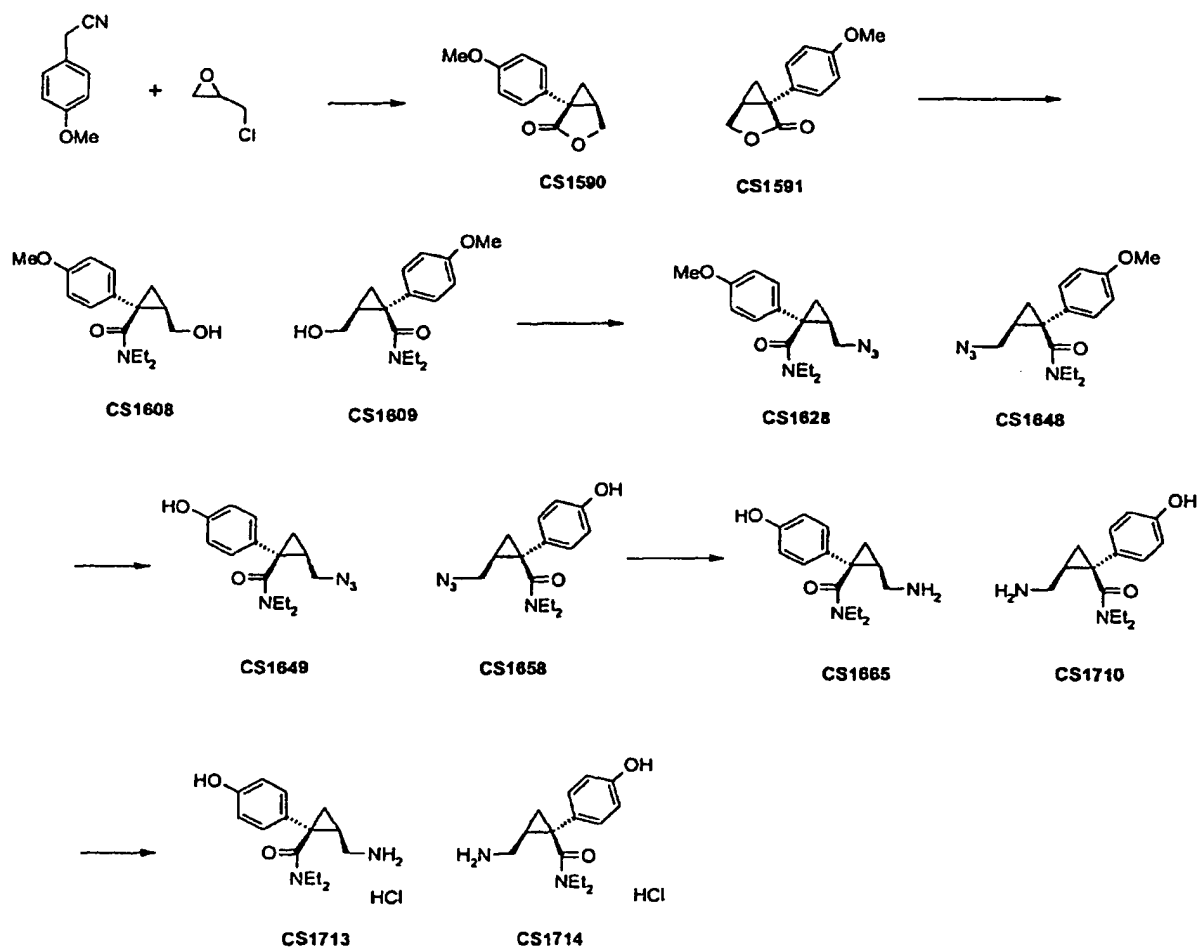


Figure 2

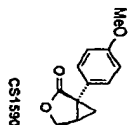


Figure 3

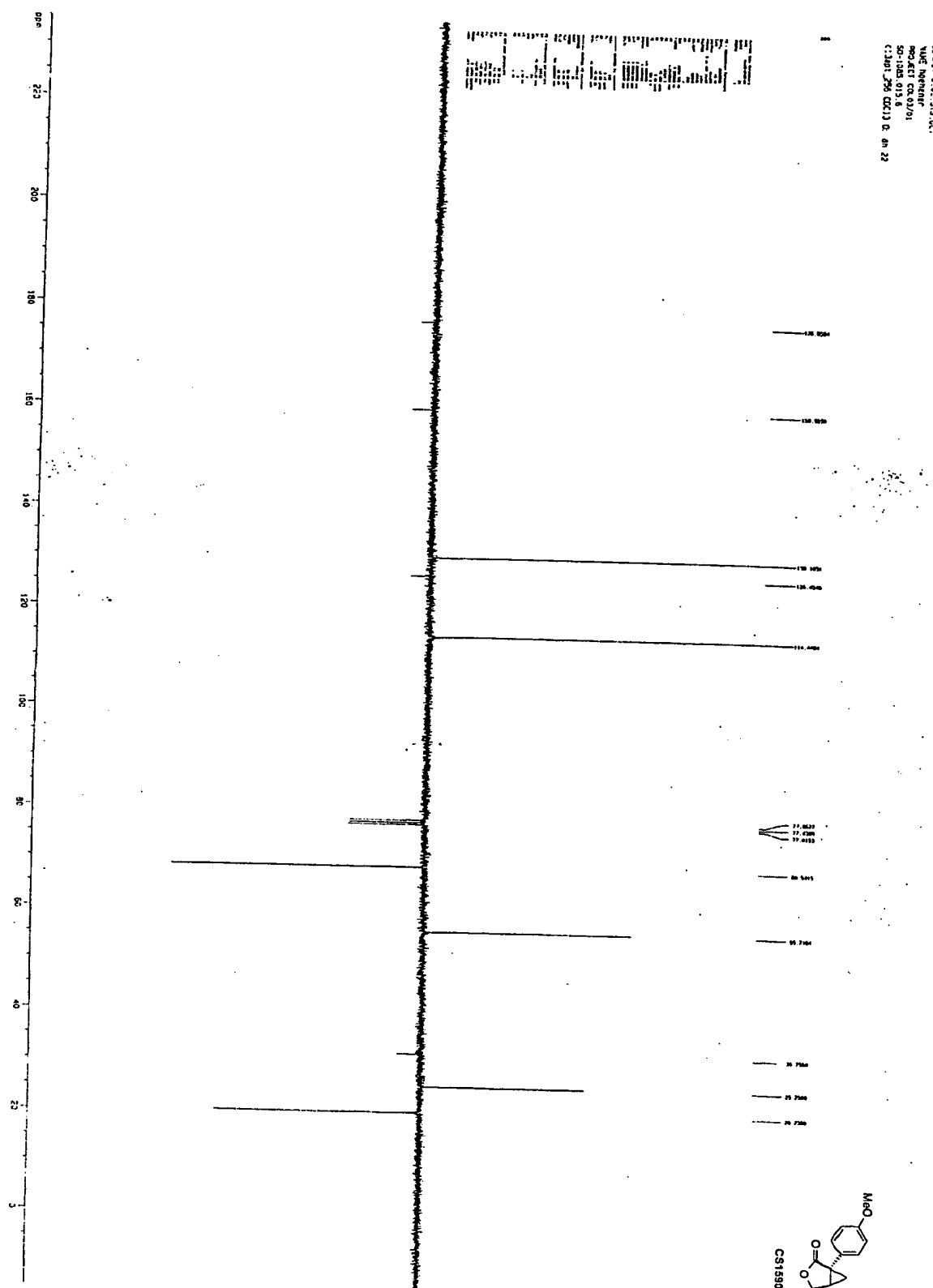


Figure 4

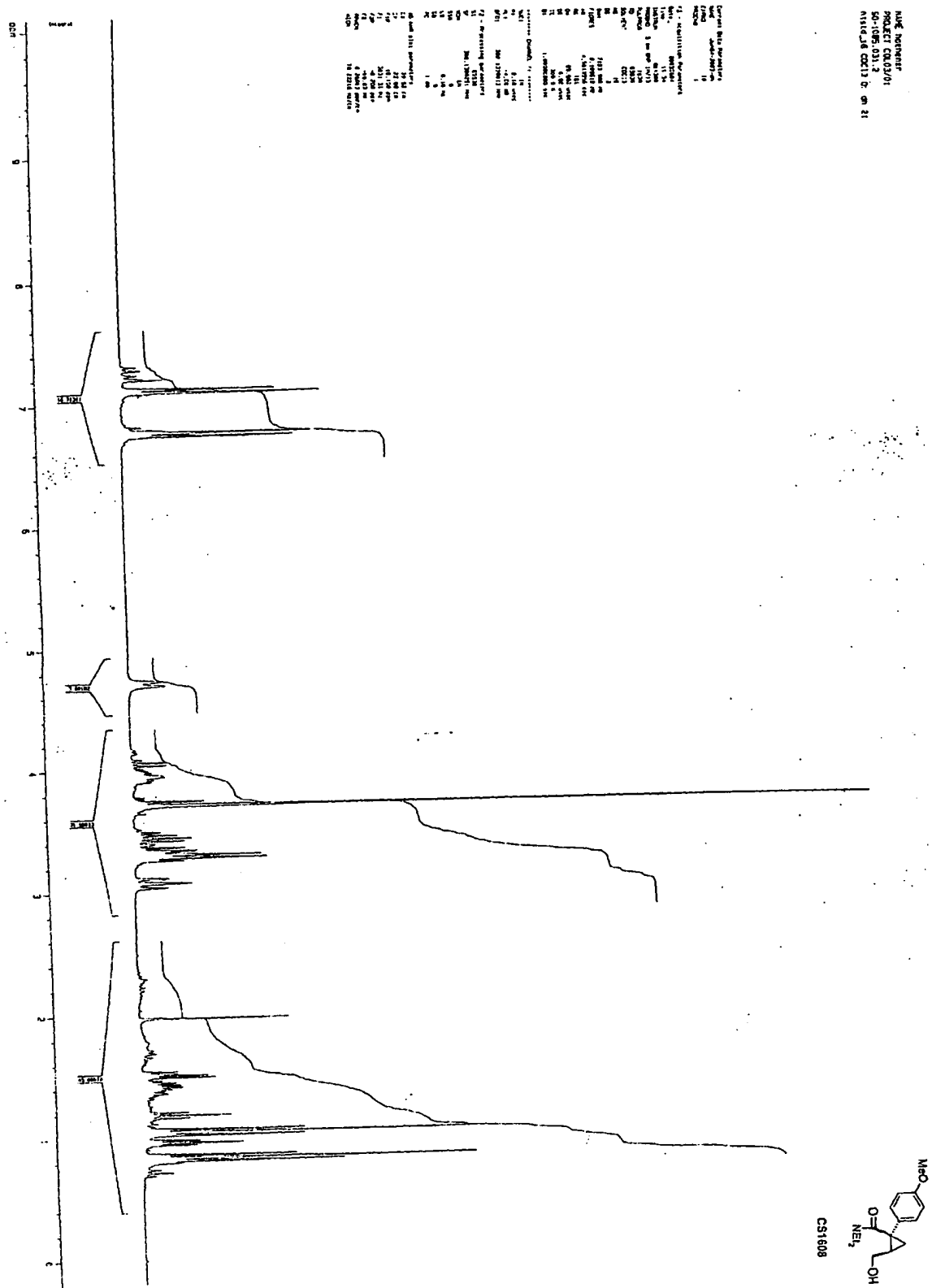


Figure 5

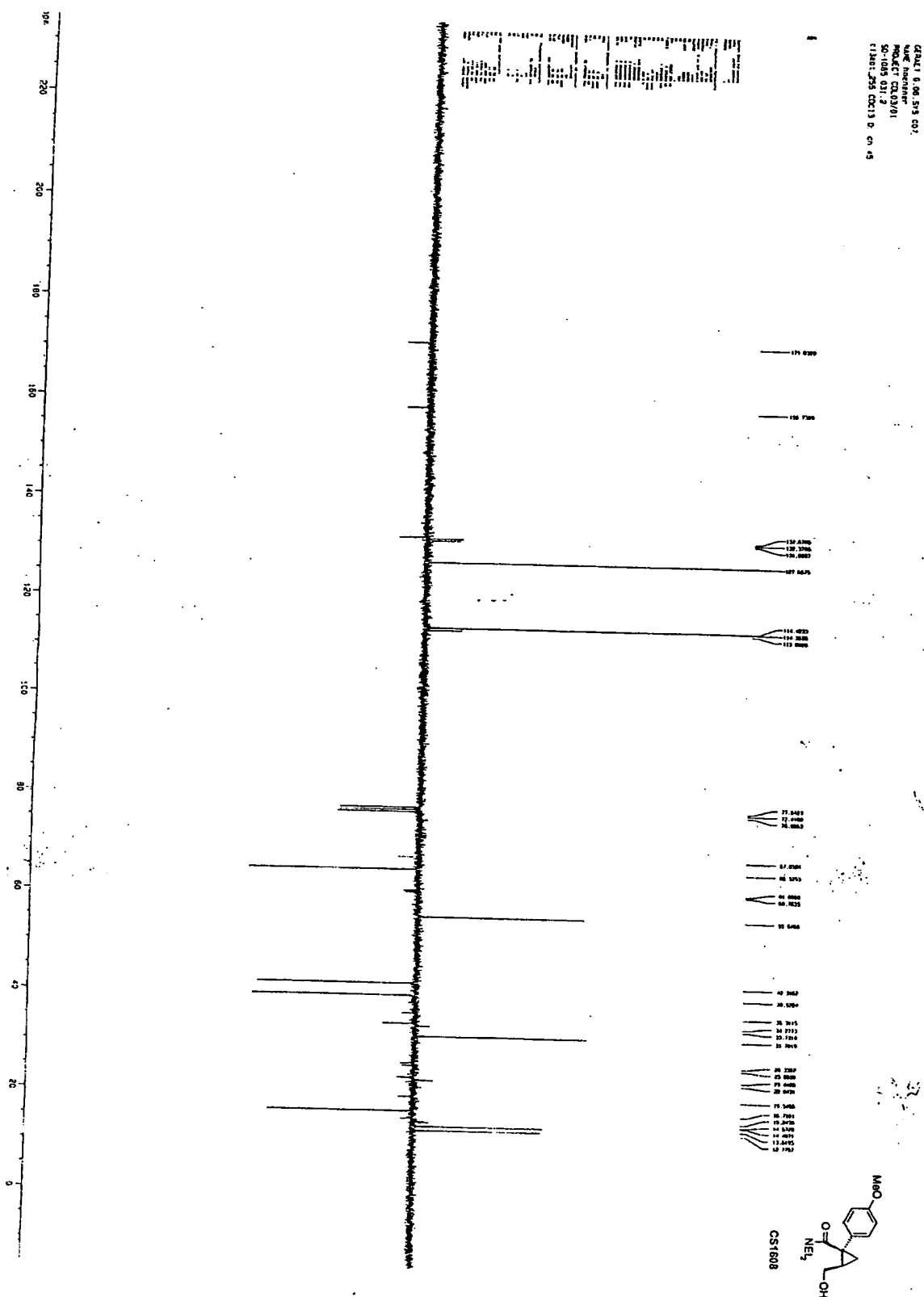


Figure 6

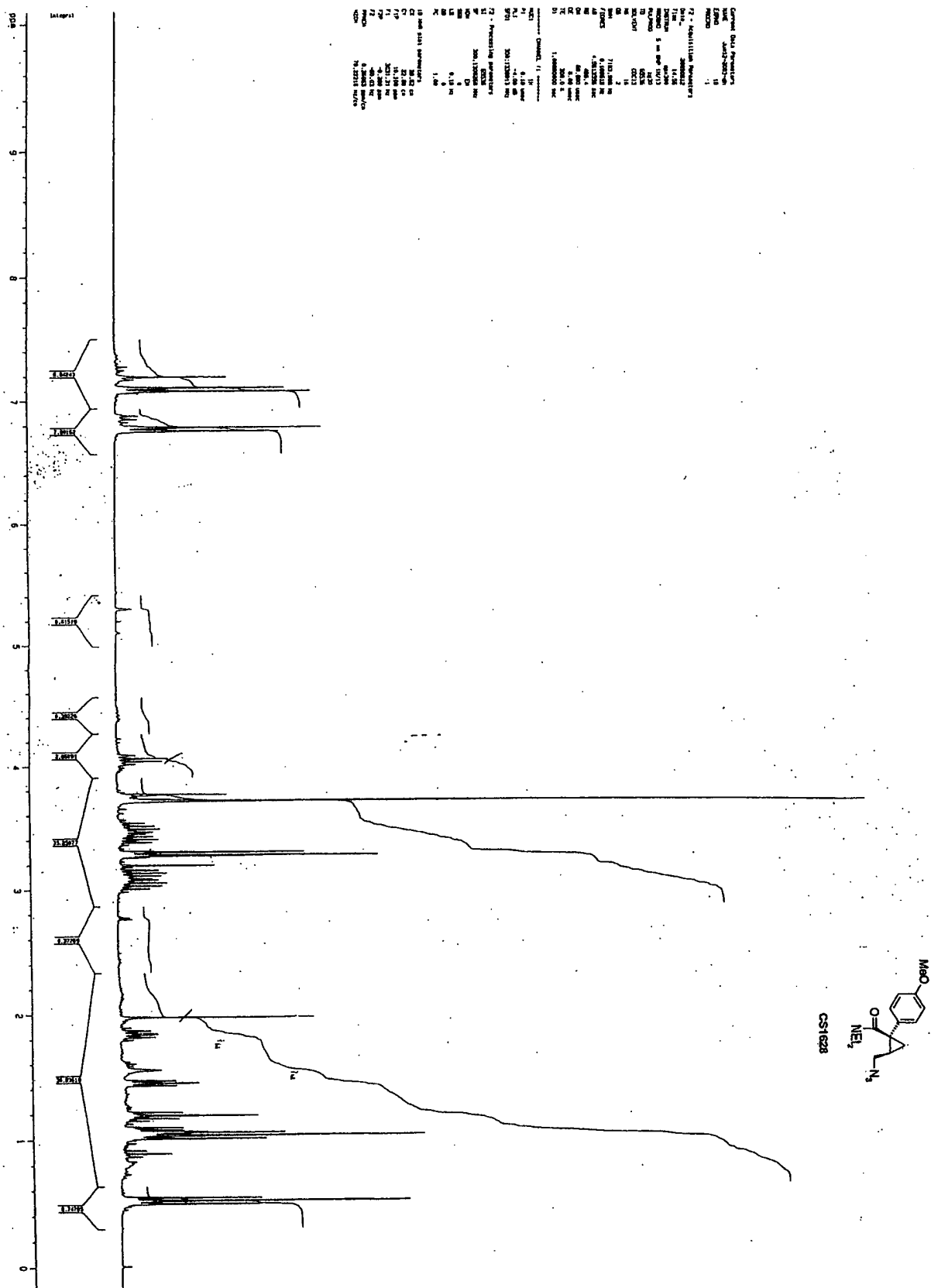


Figure 7

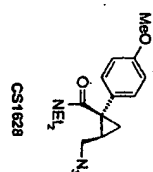
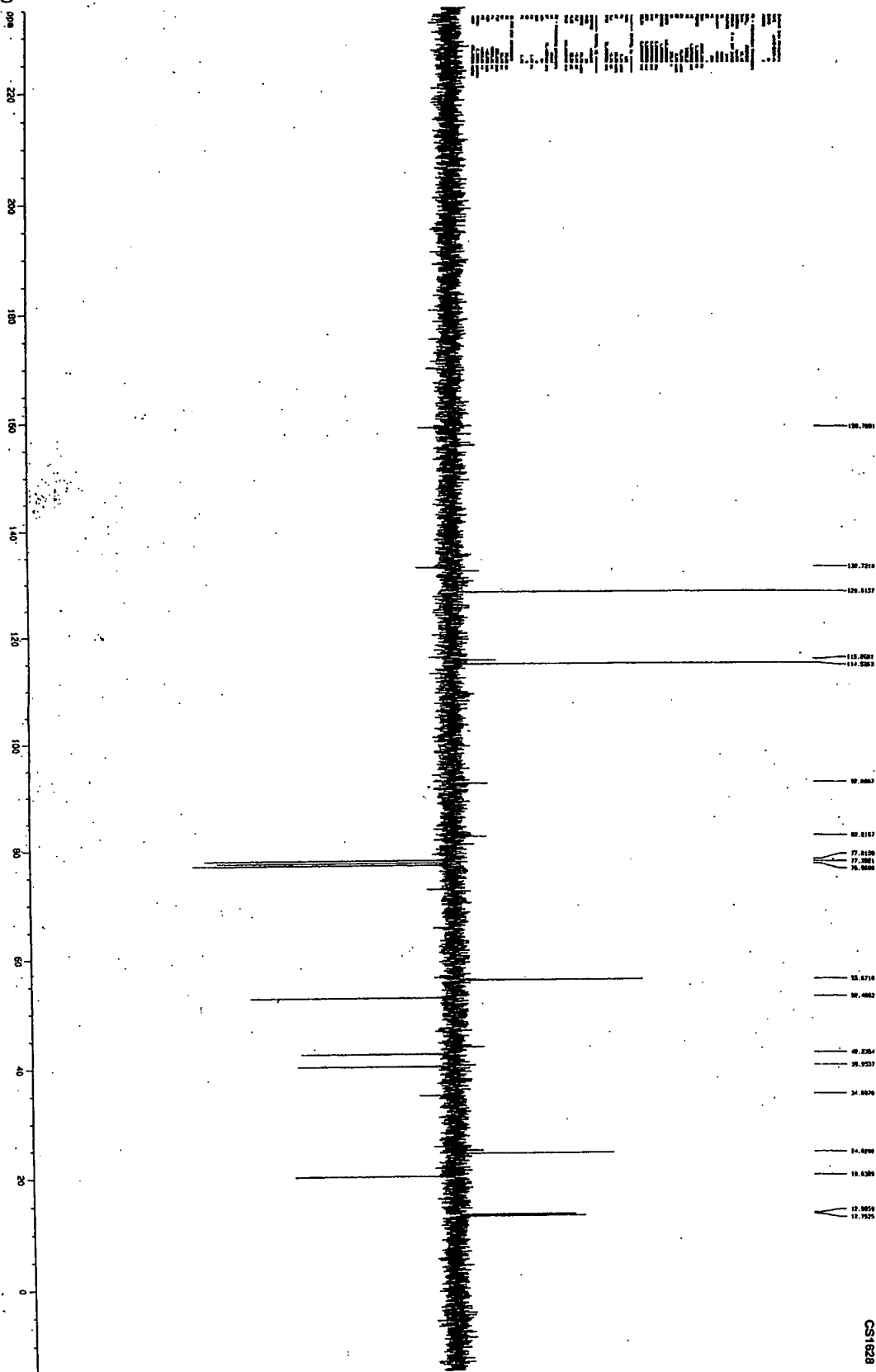


Figure 8

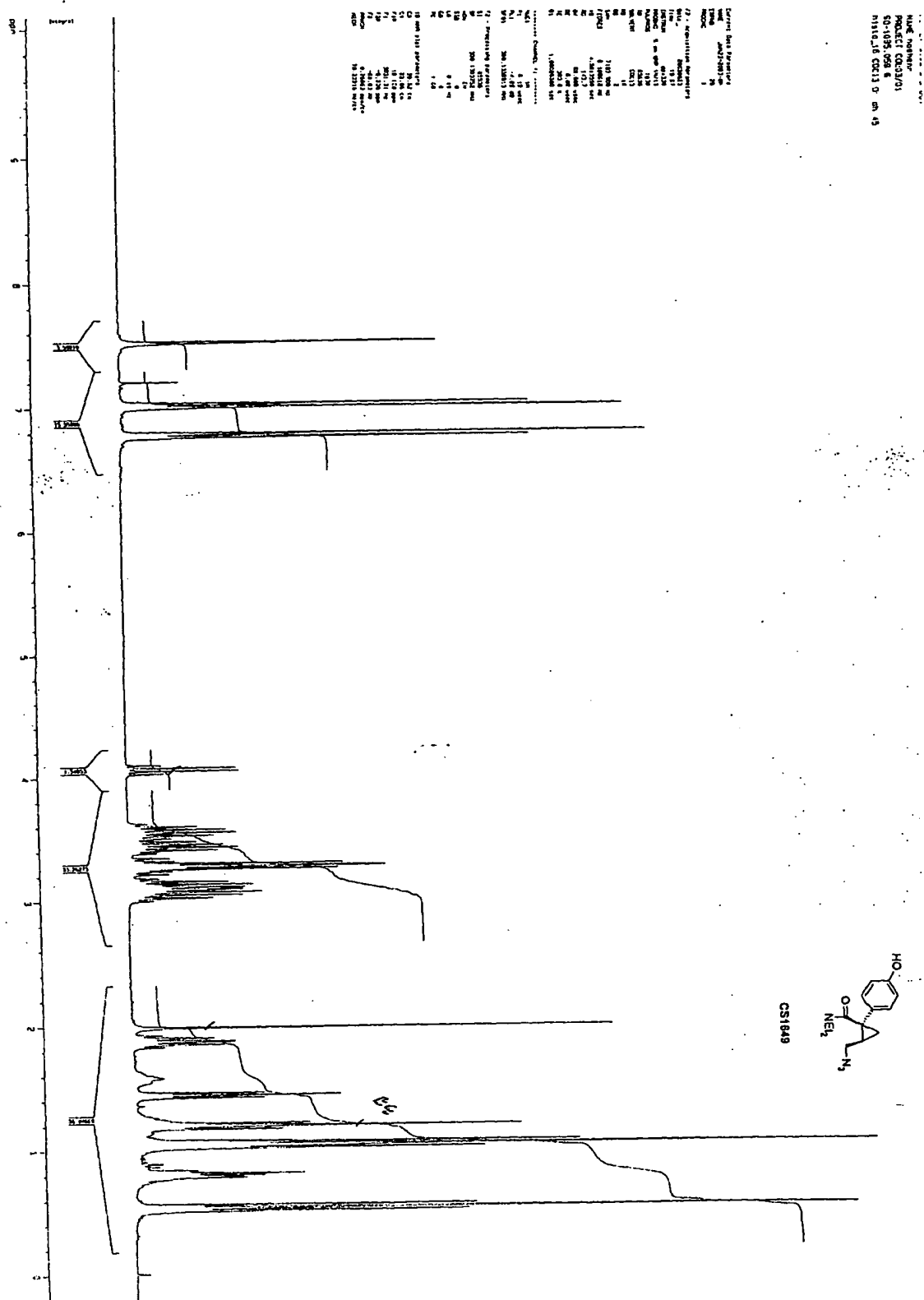


Figure 9

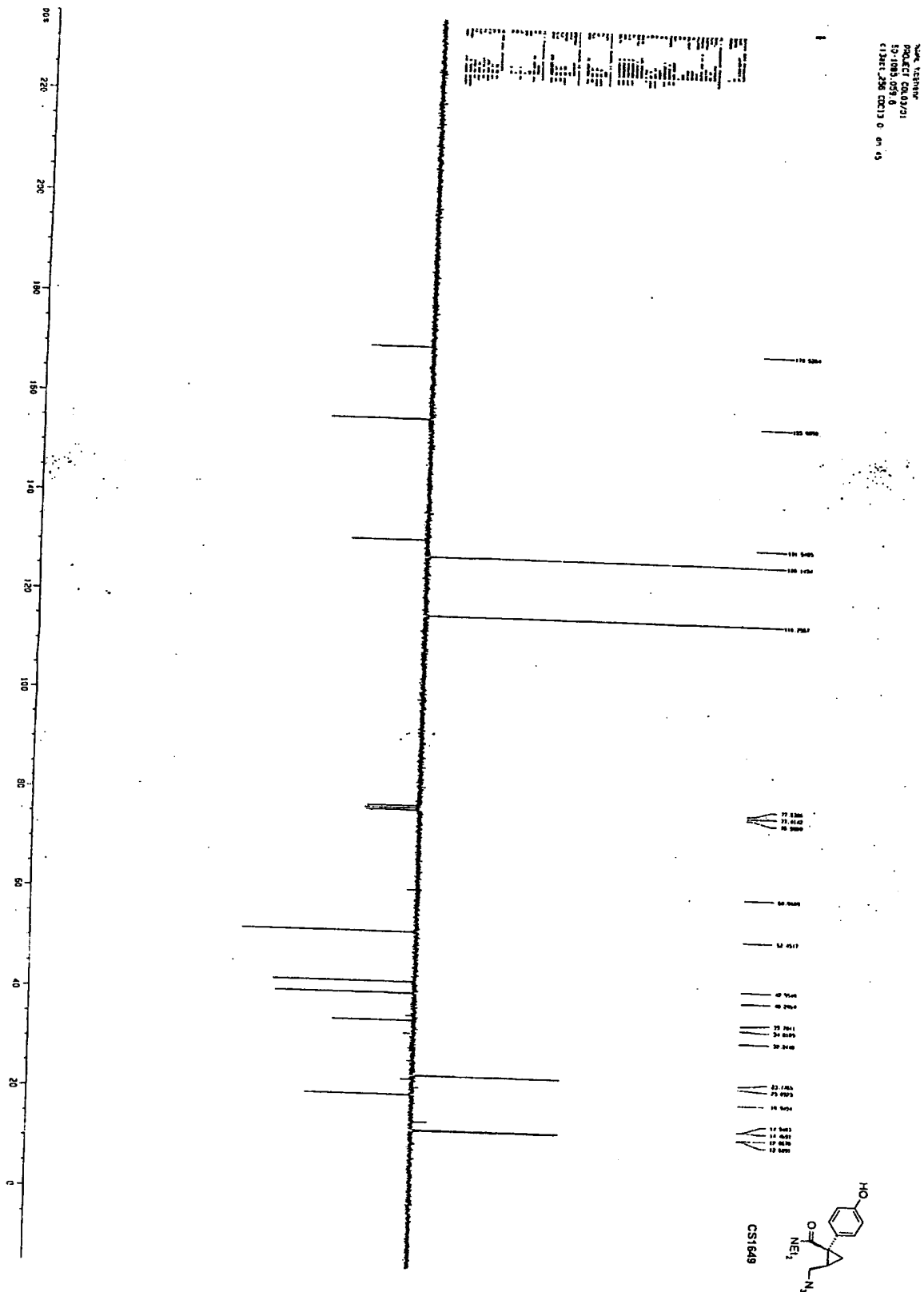


Figure 10

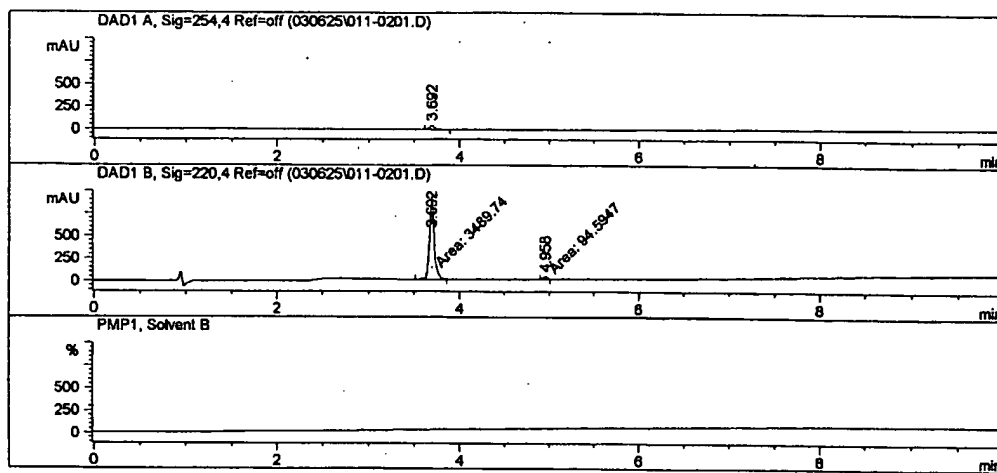
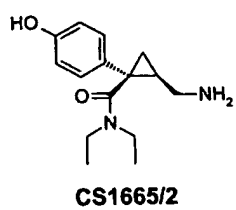


Figure 11

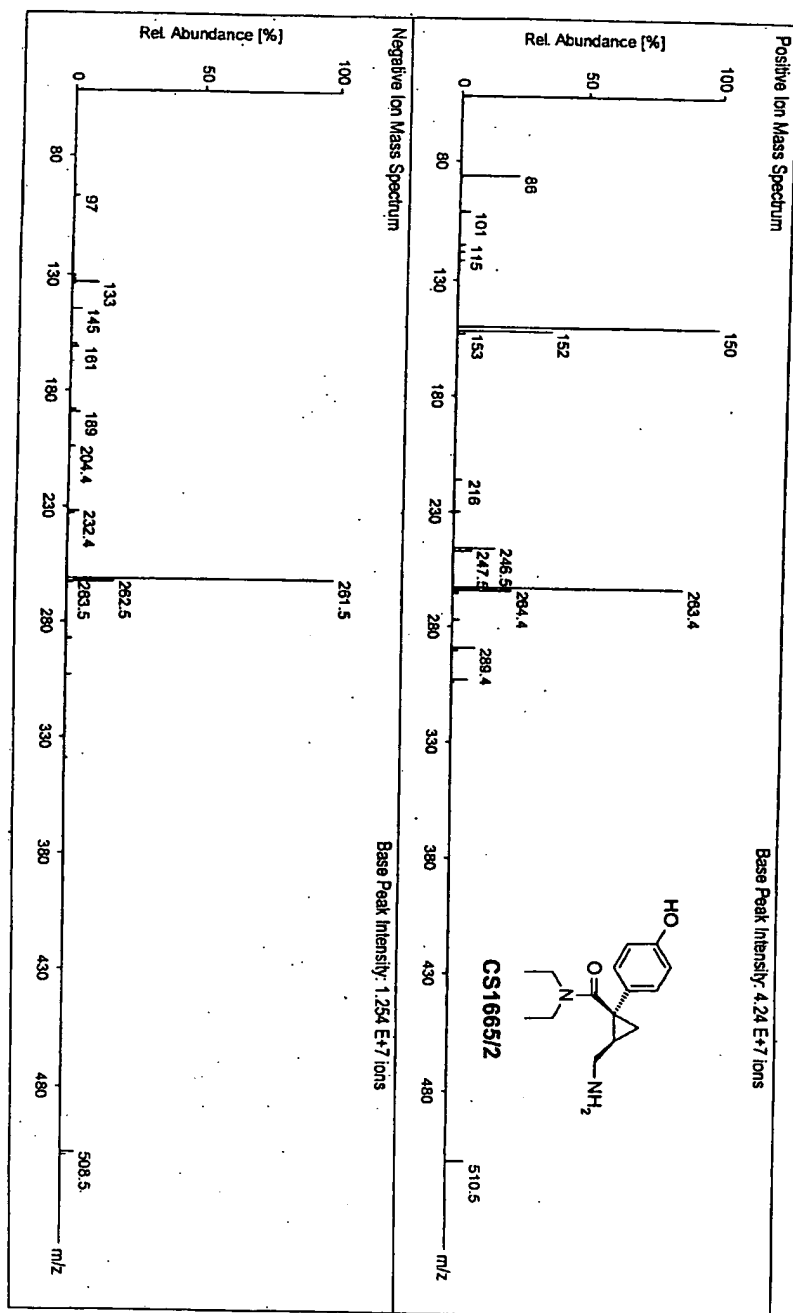


Figure 12

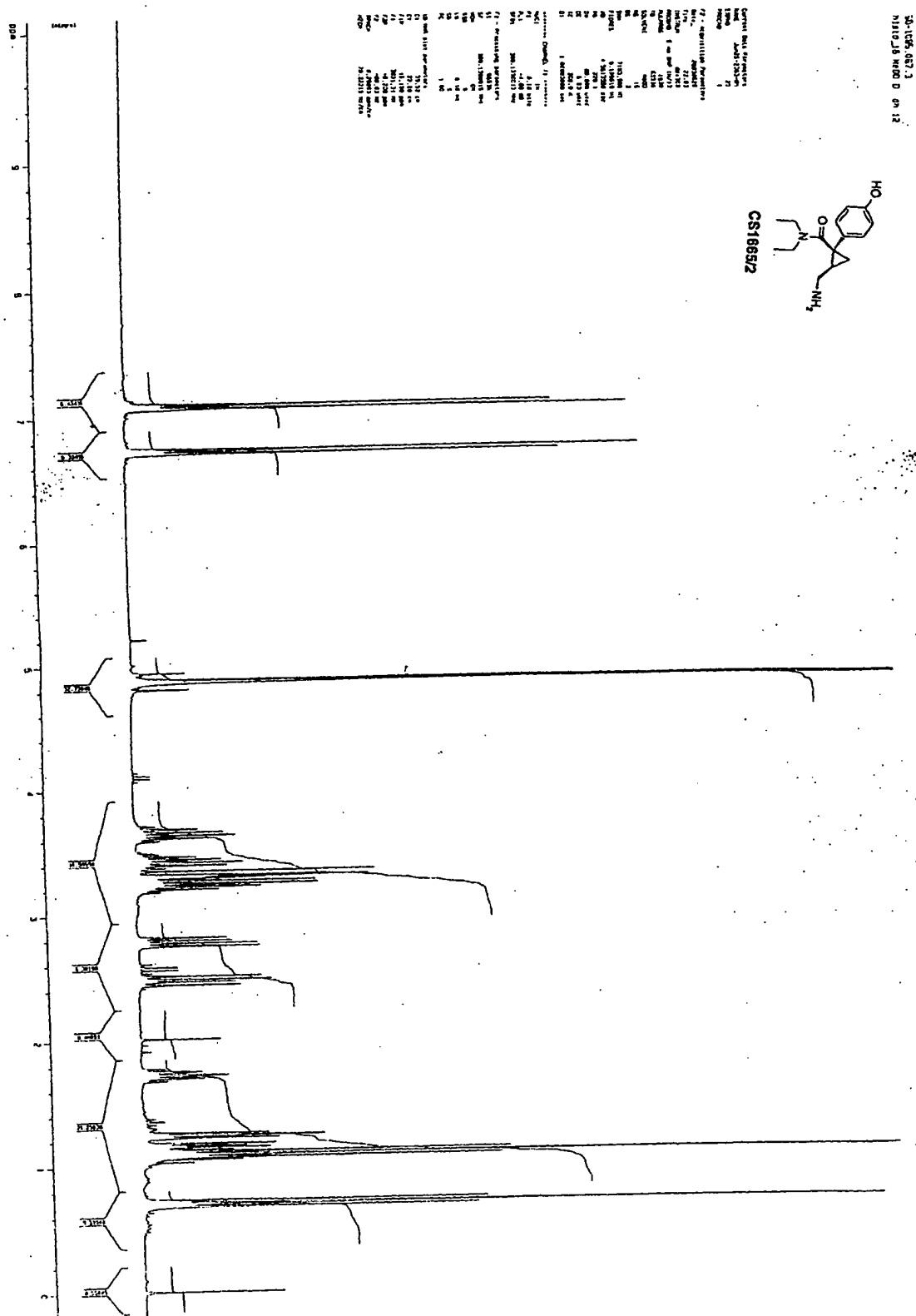


Figure 13

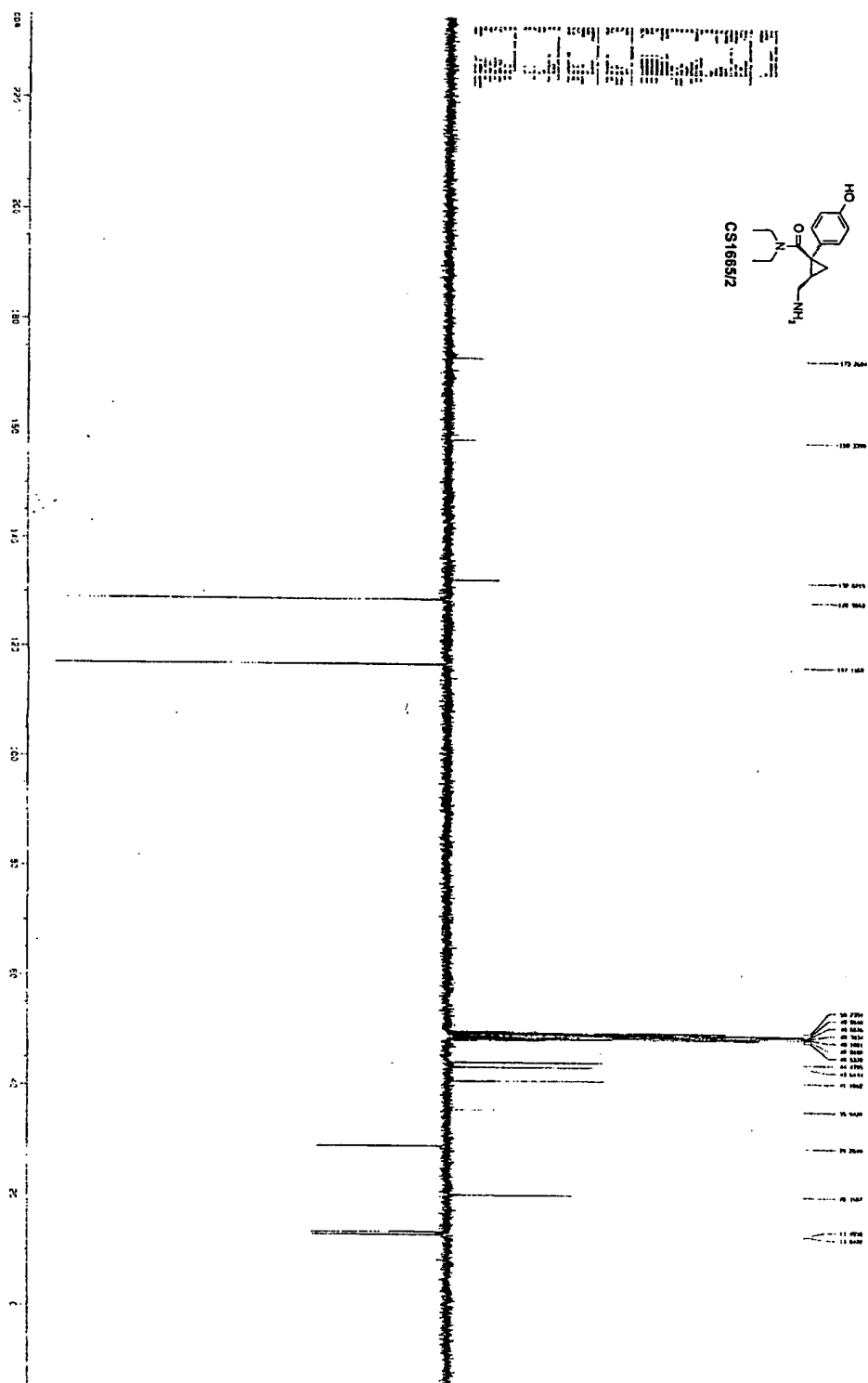
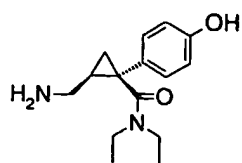


Figure 14



CS1710/1

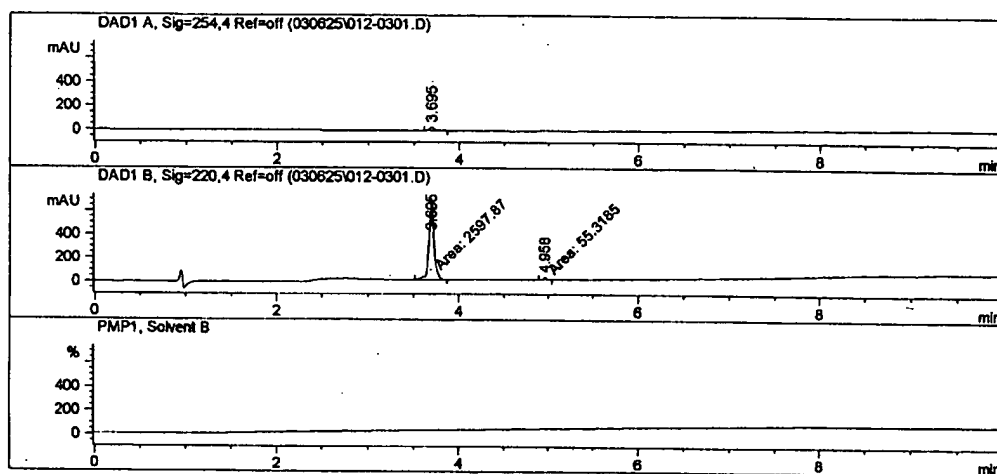


Figure 15

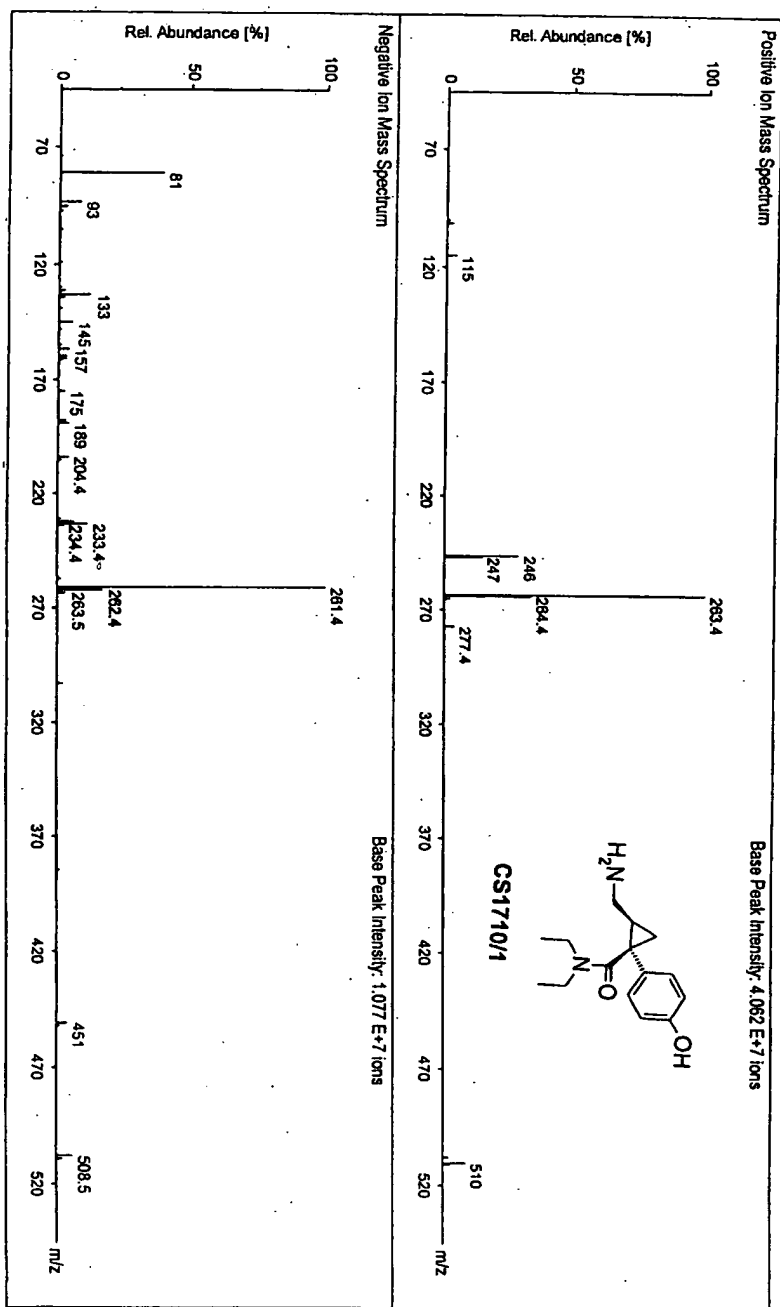


Figure 16

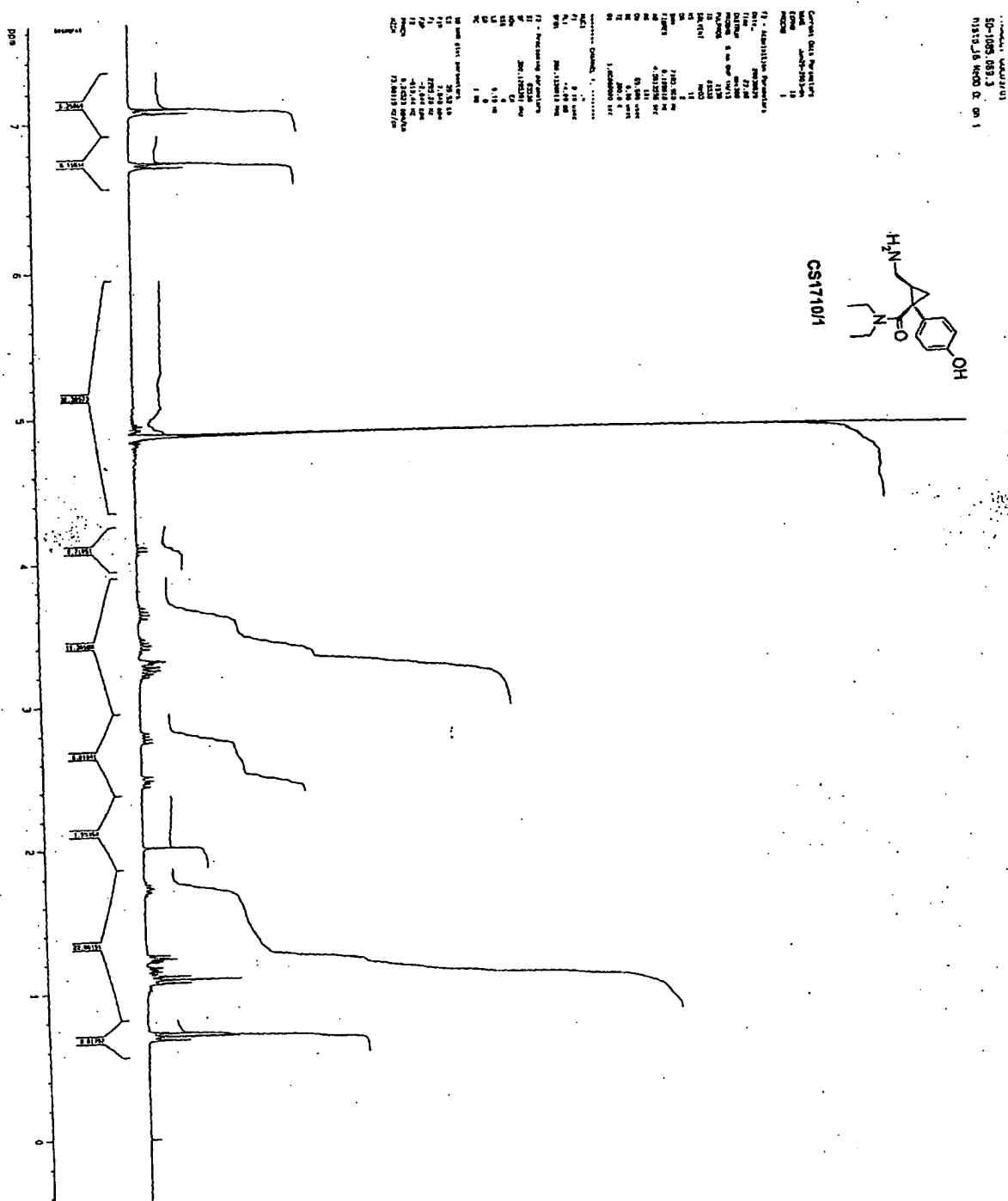


Figure 17

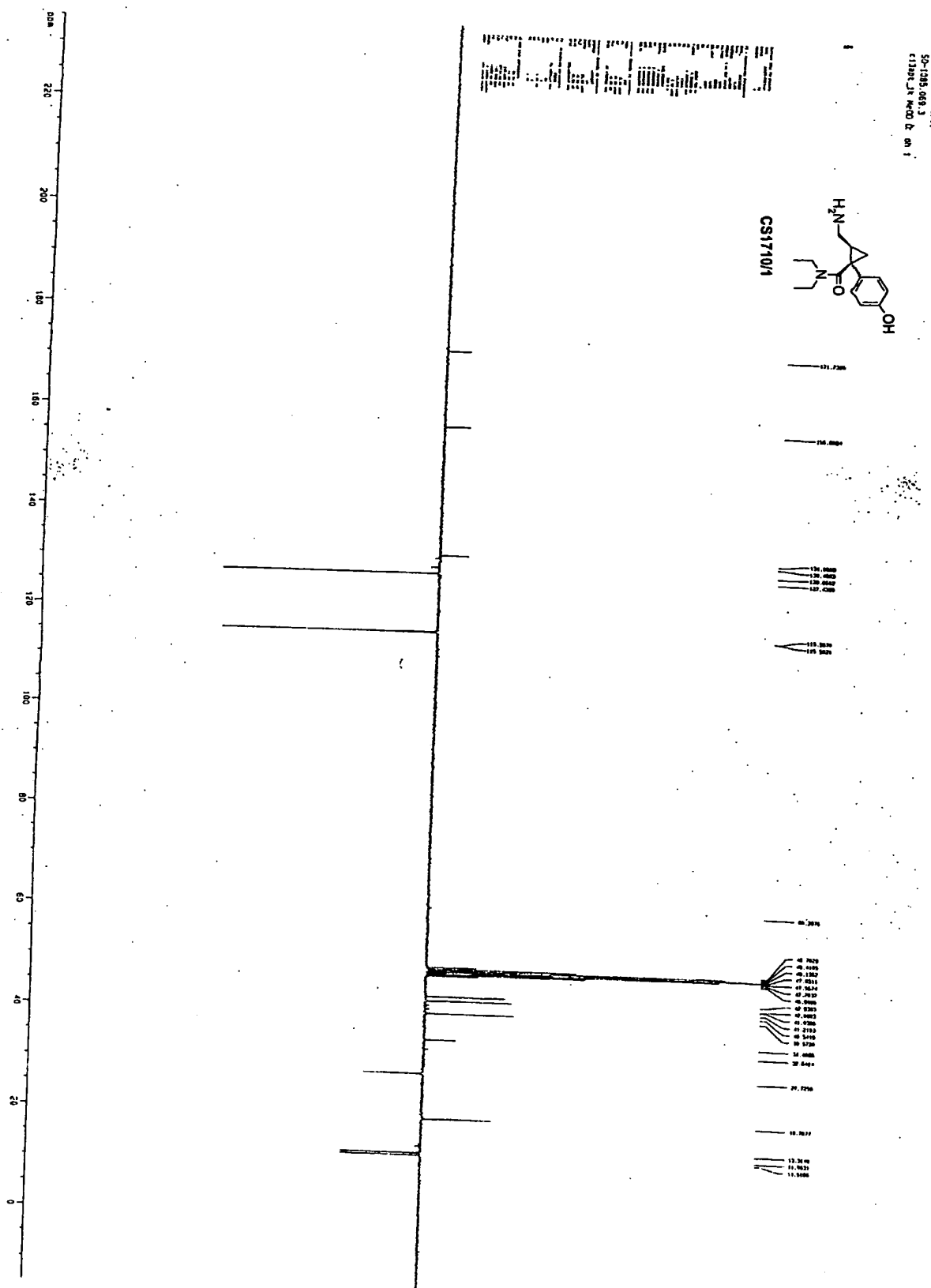
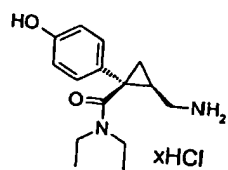


Figure 18



CS1713/1

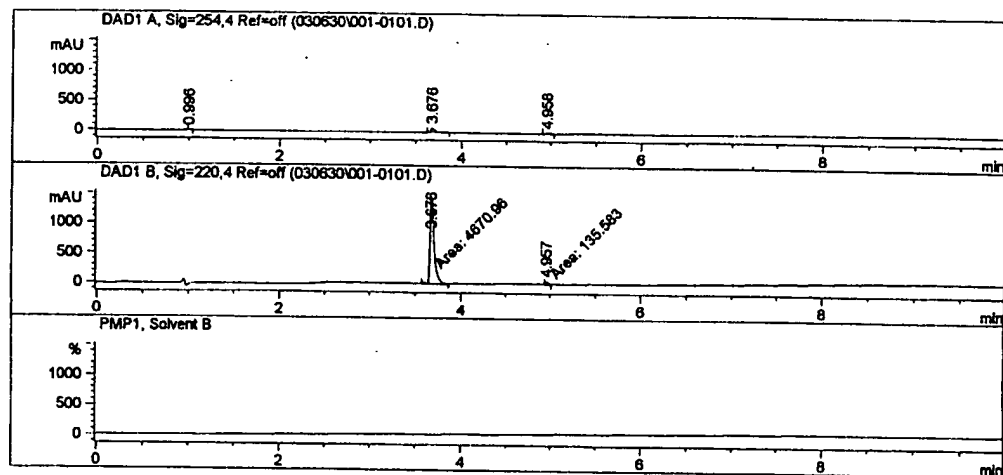


Figure 19

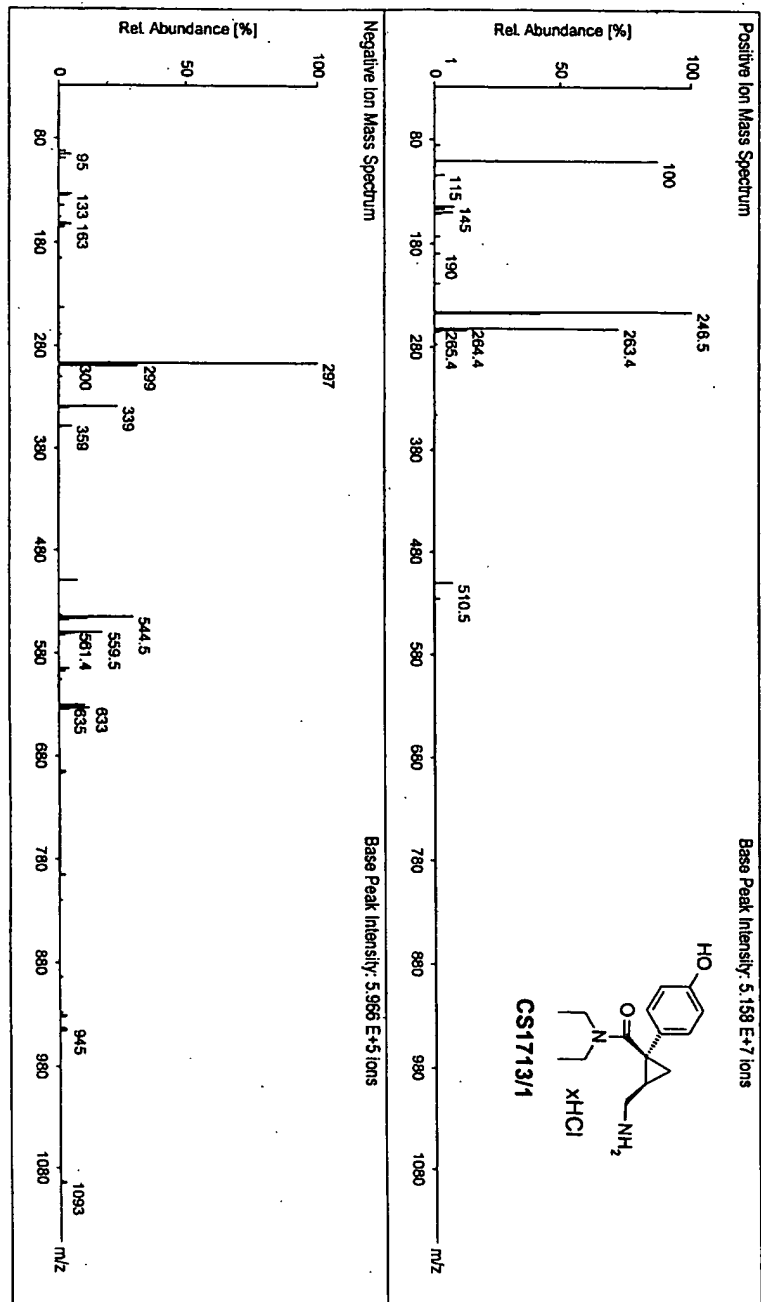


Figure 20

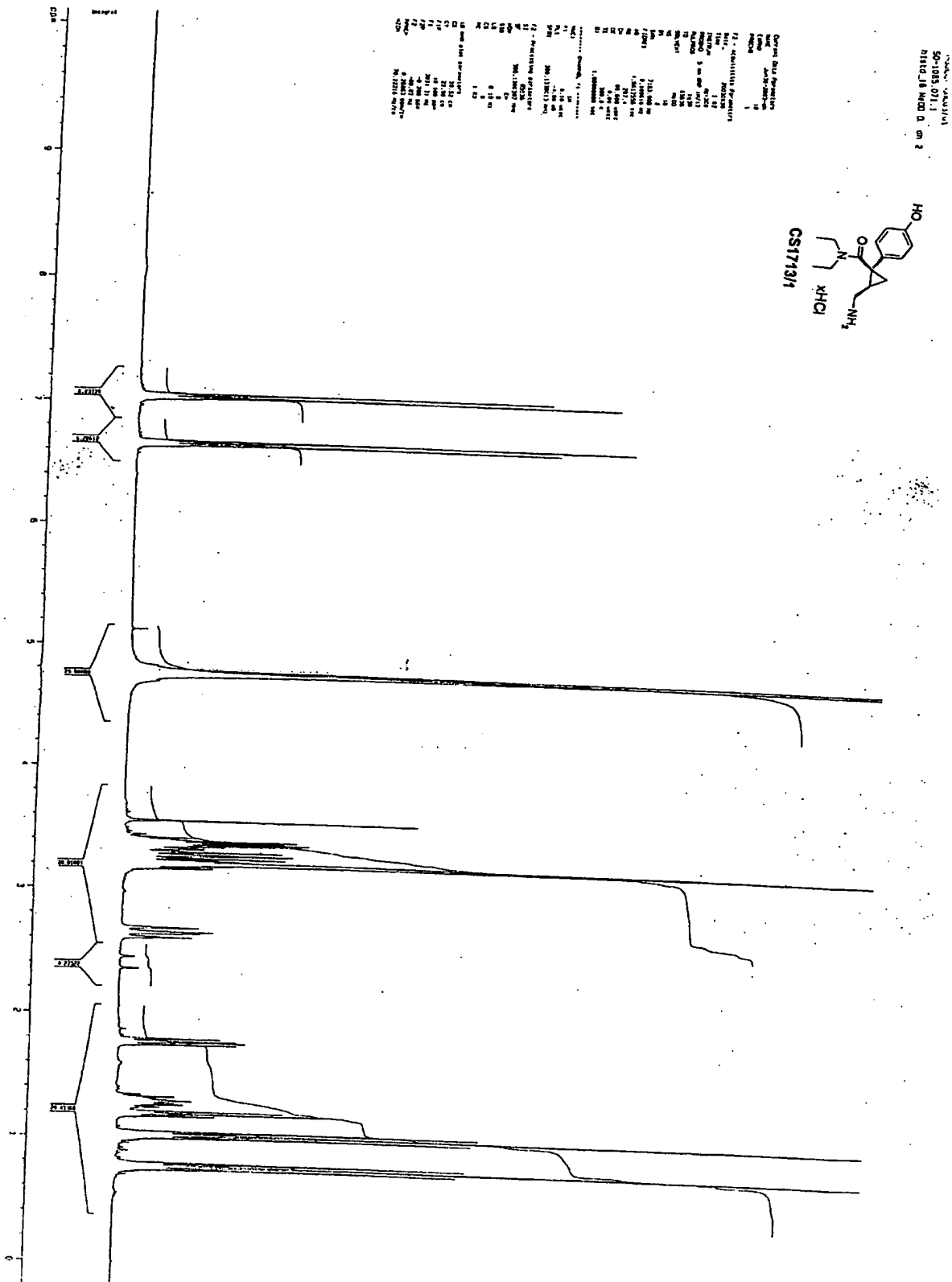


Figure 21

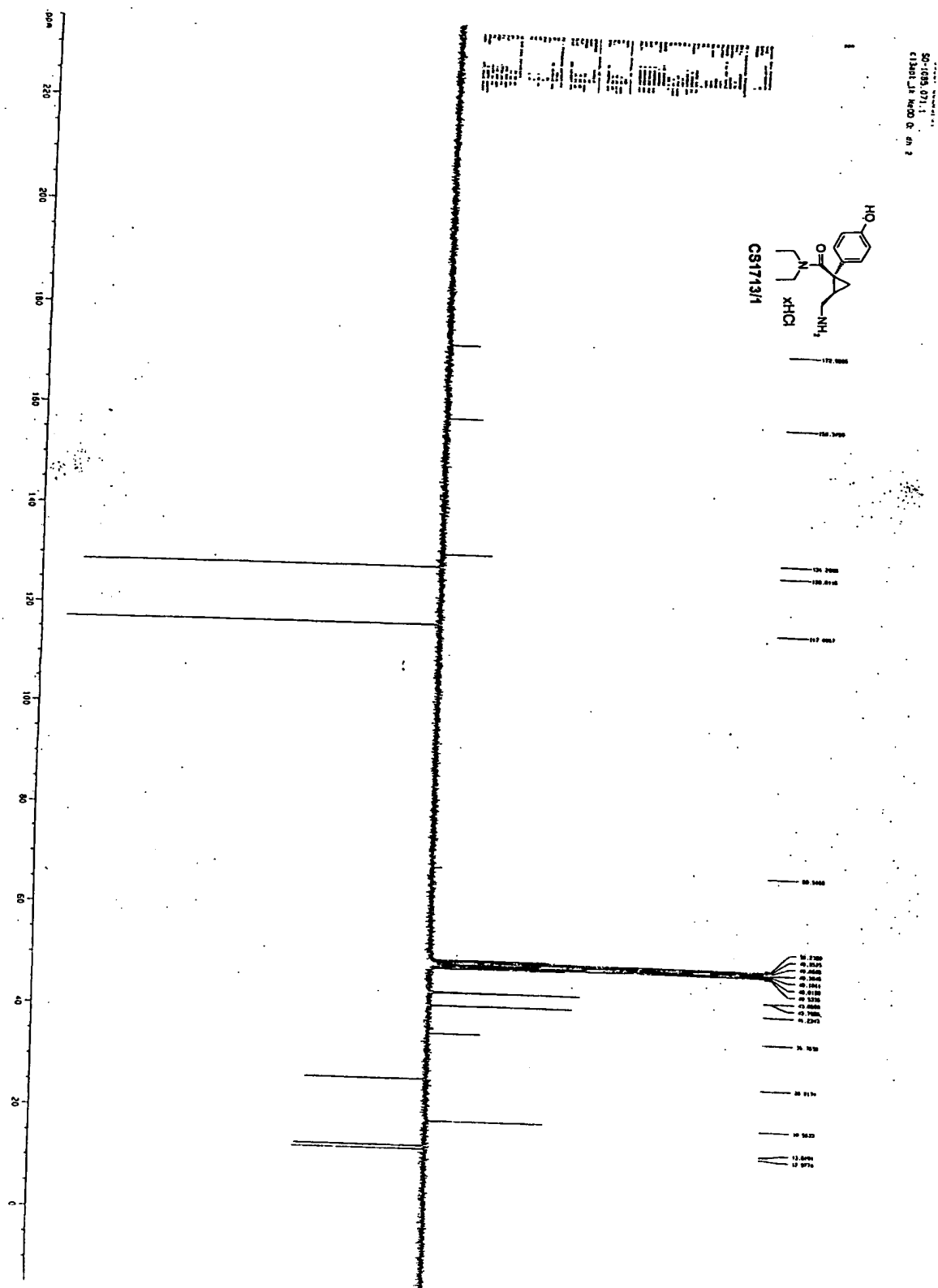
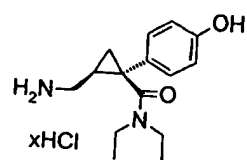


Figure 22



CS1714/1

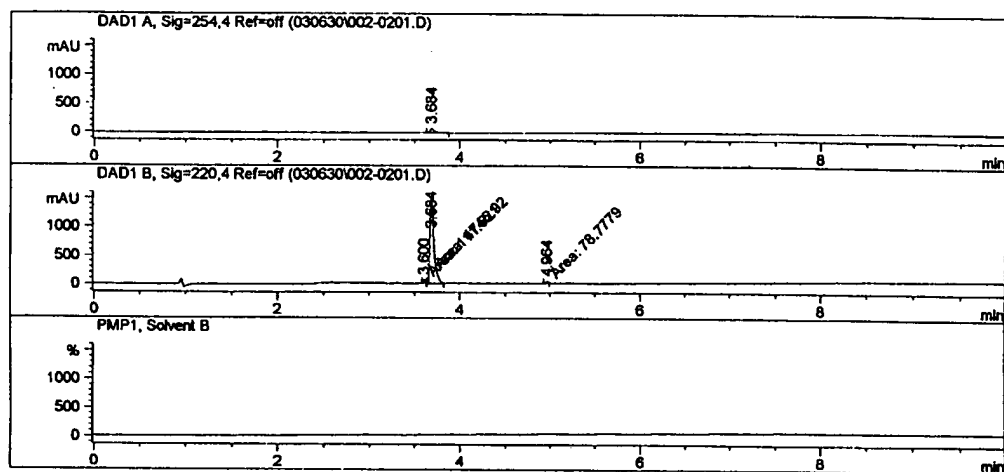


Figure 23

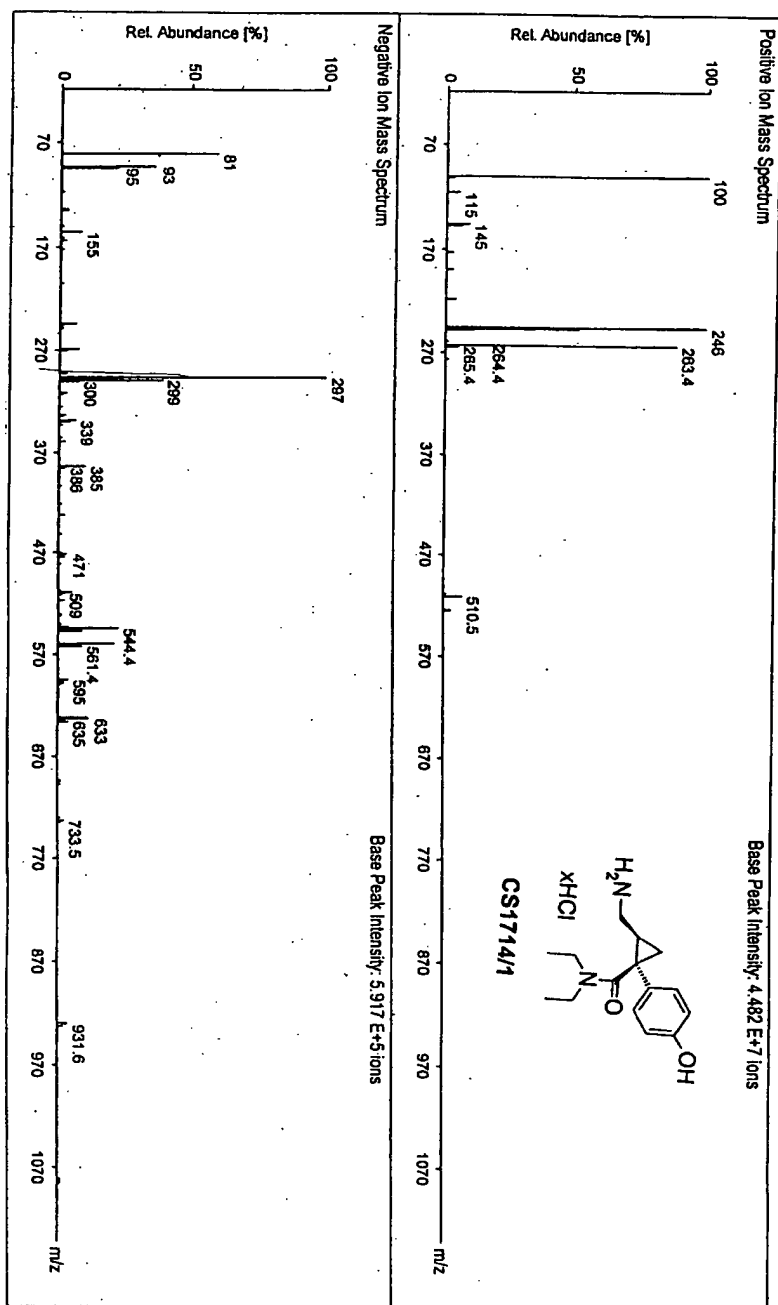


Figure 24

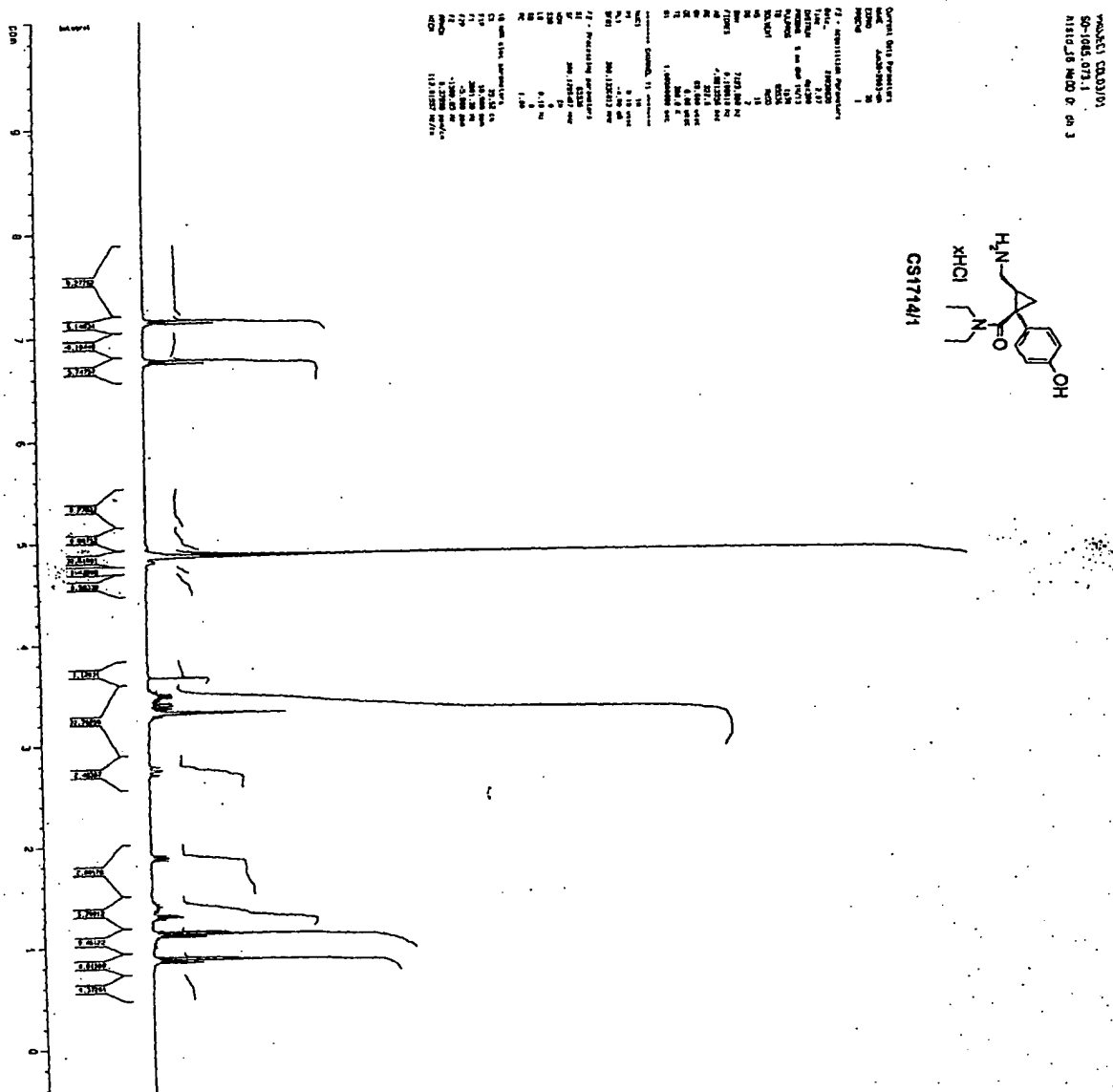


Figure 25

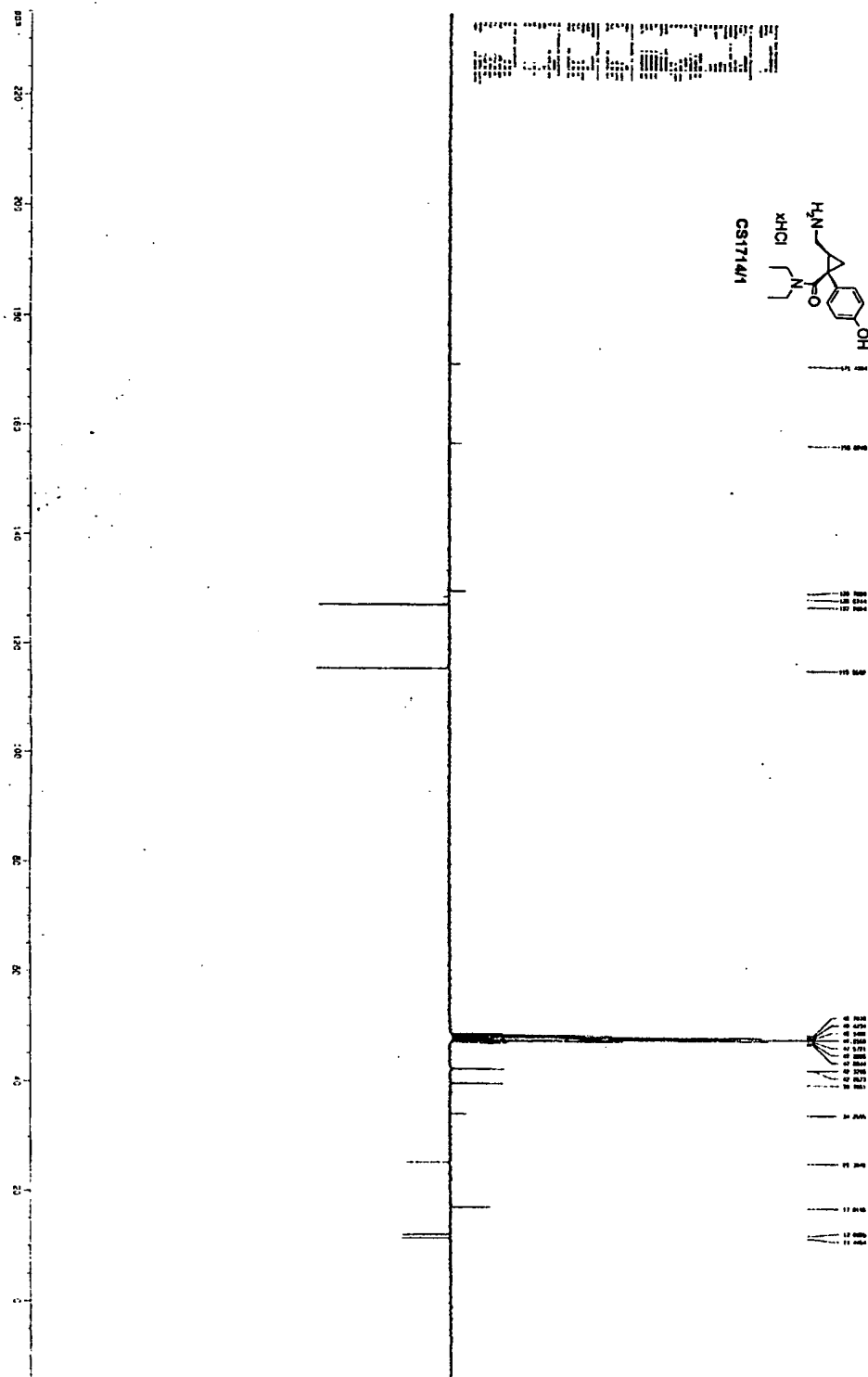


Figure 26

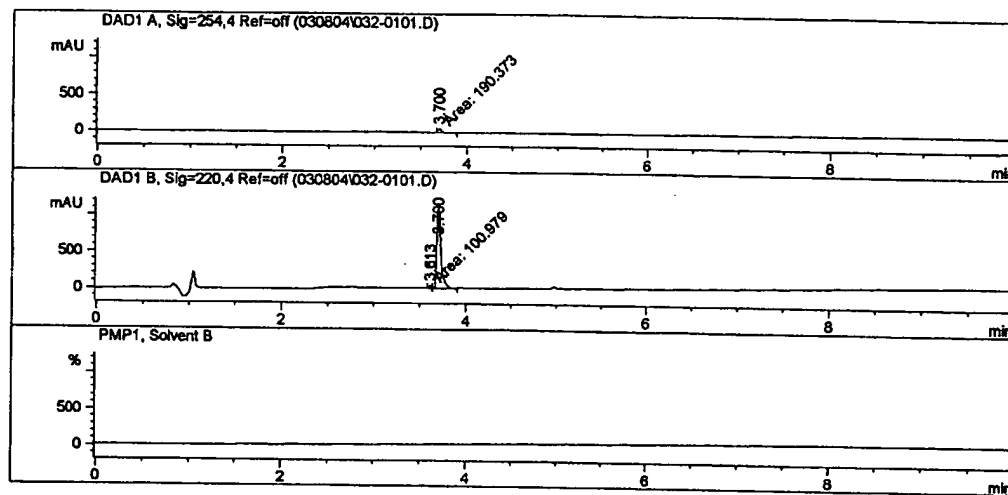


Figure 27

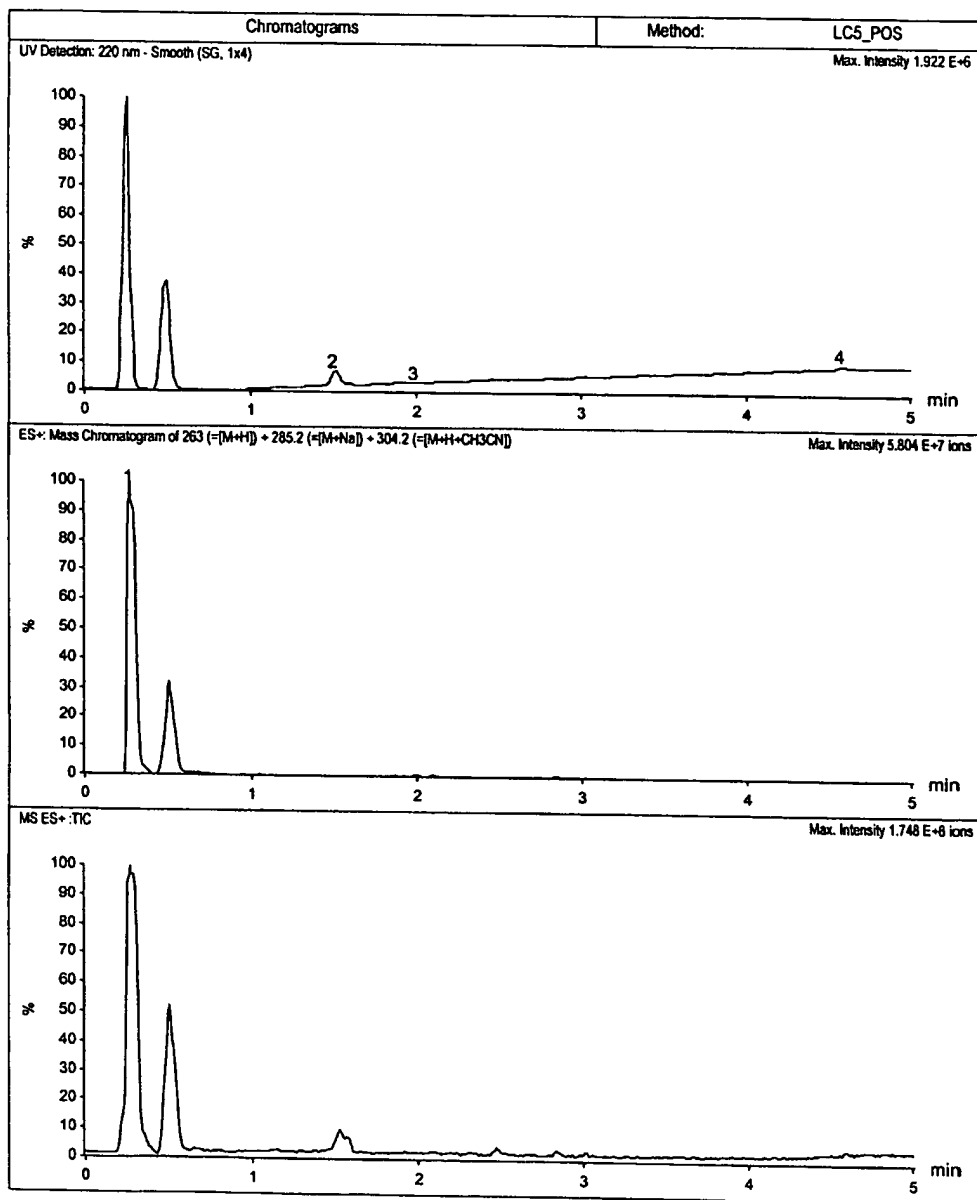


Figure 28

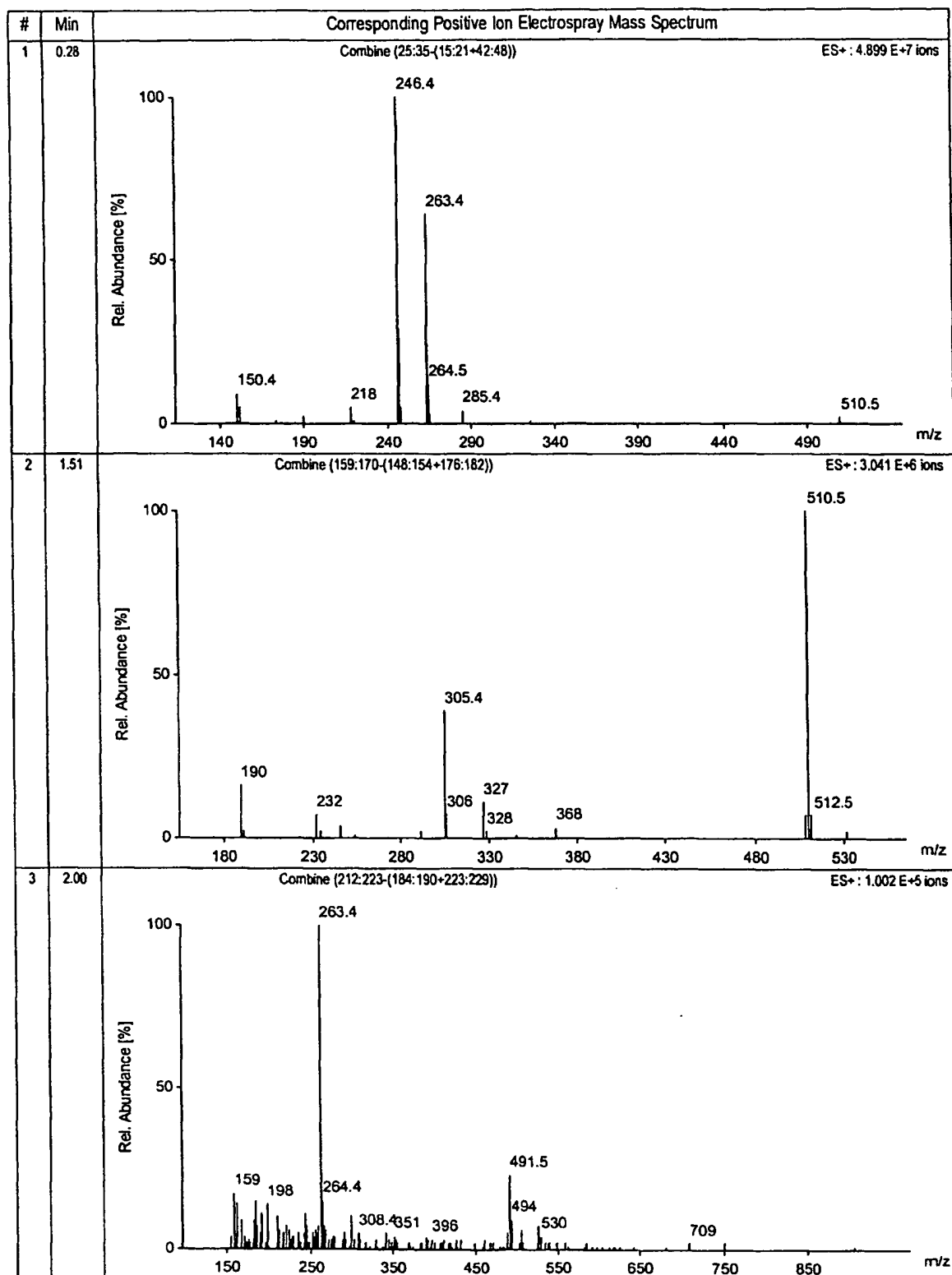


Figure 29

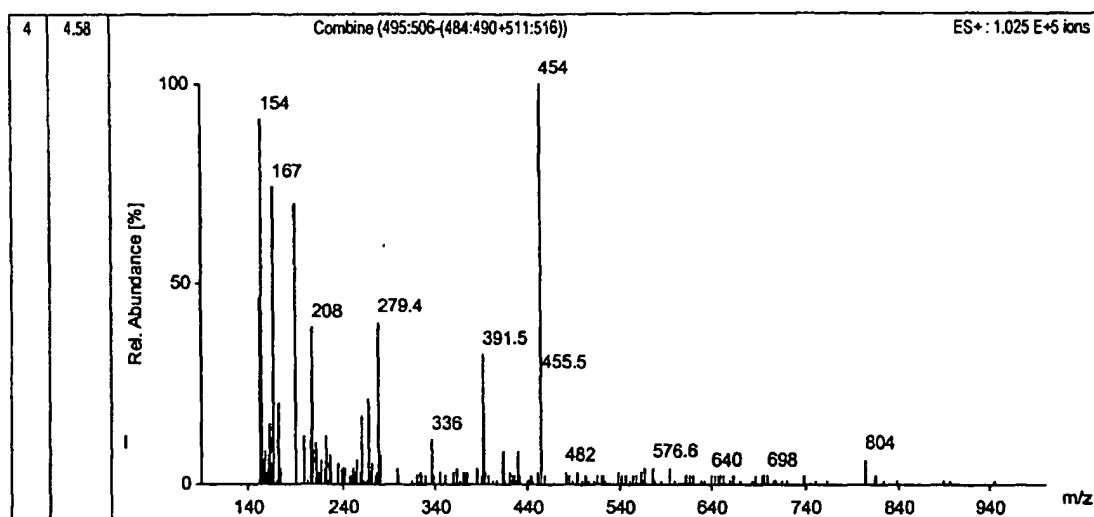
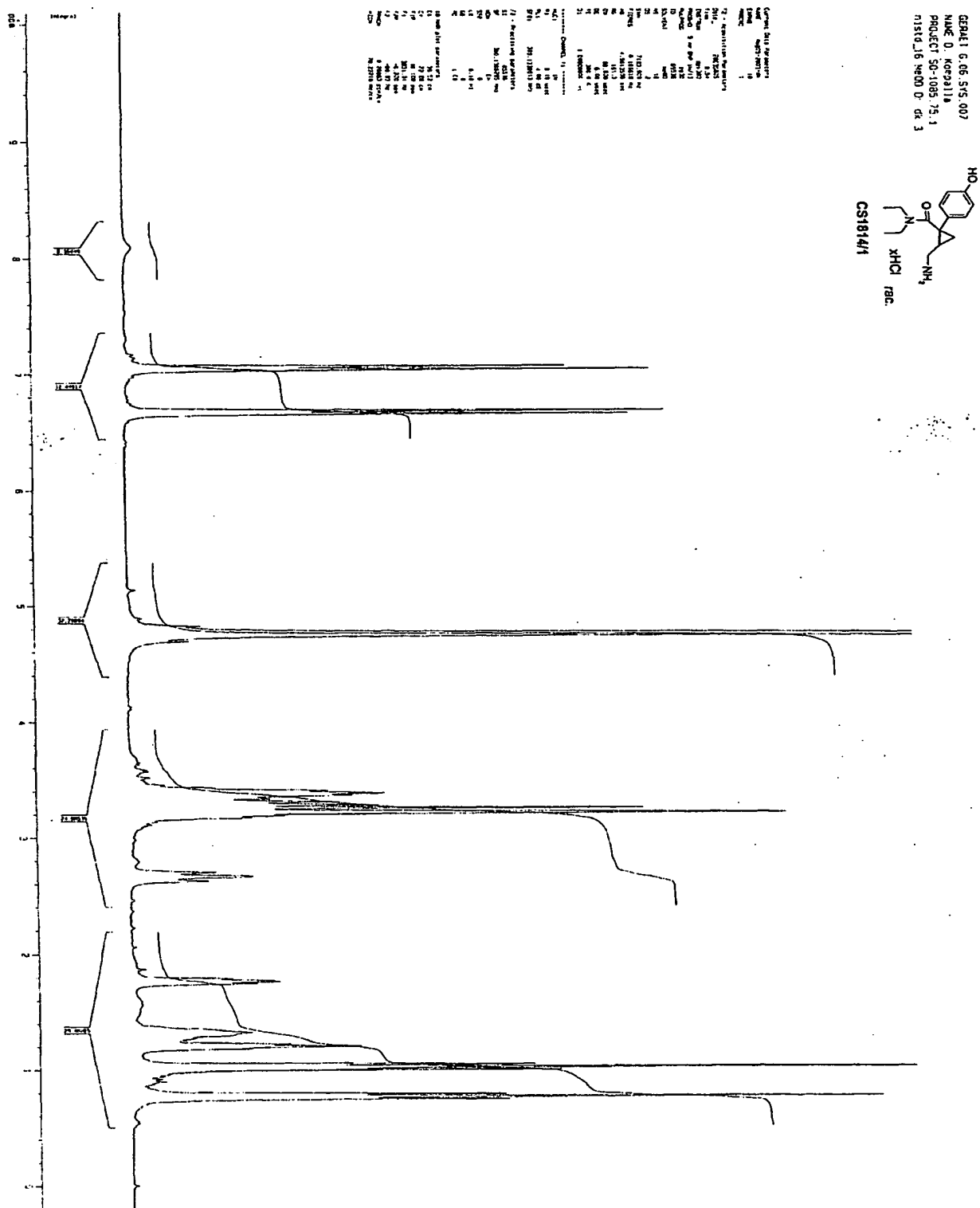


Figure 30



Chemical structure of **CS181441** (racemic) is shown, which is a hydroxy-phenyl-ethyl-amine derivative. The structure is labeled as **CS181441** and **XHCl rac.**

The ¹³C NMR spectrum displays chemical shifts (ppm) on the x-axis, ranging from 0 to 220. The spectrum shows several peaks, including a large peak at approximately 170 ppm, and smaller peaks at approximately 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, and 0 ppm.

Figure 32

CAT. #	TARGET	BATCH*	SPP.	n=	CONC.	†% INHIBITION						IC ₅₀	K _i	n _H	R
						-100	-50	0	50	100	%				
118050	CYP450, 1A2	93172	hum	2	10 µM	1									
118070	CYP450, 2C19	93174	hum	2	10 µM	13									
118060	CYP450, 2C9	93173	hum	2	10 µM	7									
118080	CYP450, 2D6	93175	hum	2	10 µM	16									
118090	CYP450, 3A4	92943	hum	2	10 µM	21									
200510	Adenosine A ₁	92728	hum	2	10 µM	-5									
200610	Adenosine A _{2A}	92729	hum	2	10 µM	-2									
203100	Adrenergic α _{1A}	92918	rat	2	10 µM	16									
203200	Adrenergic α _{1B}	92919	rat	2	10 µM	5									
203400	Adrenergic α _{1D}	92920	hum	2	10 µM	10									
203620	Adrenergic α _{2A}	92621	hum	2	10 µM	15									
203710	Adrenergic α _{2B}	92922	hum	2	10 µM	14									
204010	Adrenergic β ₁	92731	hum	2	10 µM	8									
204110	Adrenergic β ₂	92732	hum	2	10 µM	3									
212500	Bradykinin B ₁	92644	hum	2	10 µM	10									
212610	Bradykinin B ₂	92828	hum	2	10 µM	20									
214510	Calcium Channel L-Type, Benzothiazepine	92613	rat	2	10 µM	26									
214600	Calcium Channel L-Type, Dihydropyridine	92614	rat	2	10 µM	-14									
216000	Calcium Channel N-Type	92708	rat	2	10 µM	-5									
219500	Dopamine D ₁	92810	hum	2	10 µM	-4									
219600	Dopamine D _{2L}	92811	hum	2	10 µM	-4									
219800	Dopamine D ₃	92813	hum	2	10 µM	-11									
219900	Dopamine D _{4,2}	92814	hum	2	10 µM	-1									
224010	Endothelin ET _A	92735	hum	2	10 µM	0									
224110	Endothelin ET _B	92736	hum	2	10 µM	-5									
225500	Epidermal Growth Factor (EGF)	92641	hum	2	10 µM	3									
226010	Estrogen ERα	92633	hum	2	10 µM	7									
226500	GABA _A , Agonist Site	92616	rat	2	10 µM	-10									
226600	GABA _A , Benzodiazepine, Central	92830	rat	2	10 µM	-3									
228510	GABA _A , Non-Selective	92715	rat	2	10 µM	9									
232010	Glucocorticoid	92894	hum	2	10 µM	0									

*Batch: Represents compounds tested concurrently in the same assay(s).

†Results with ≥ 50% stimulation or inhibition are boldfaced. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

gp=guinea pig; hum=human; syh=syrian hamster

Figure 33

CAT. #	TARGET	BATCH*	SPP.	n=	CONC.	% INHIBITION					IC ₅₀	K _i	n _H	R
						-100	-50	0	50	100				
						%	↓	↓	↓	↓	↓			
232700	Glutamate, Kainate	92635	rat	2	10 μM	4								
232810	Glutamate, NMDA, Agonism	92720	rat	2	10 μM	-10								
232910	Glutamate, NMDA, Glycine	92912	rat	2	10 μM	5								
233000	Glutamate, NMDA, Phencyclidine	92636	rat	2	10 μM	0								
239610	Histamine H ₁	92617	hum	2	10 μM	-16								
239710	Histamine H ₂	92618	hum	2	10 μM	1								
239810	Histamine H ₃	92853	hum	2	10 μM	-7								
241000	Imidazoline I ₂ , Central	92836	rat	2	10 μM	-7								
243510	Interleukin IL-1, Non-Selective	92929	mous	2	10 μM	0								
250600	Leukotriene LTD ₄	92643	gp	2	10 μM	-1								
252600	Muscarinic M ₁	92840	hum	2	10 μM	2								
252700	Muscarinic M ₂	92841	hum	2	10 μM	7								
252800	Muscarinic M ₃	92842	hum	2	10 μM	-2								
257000	Neuropeptide Y ₁	92820	hum	2	10 μM	10								
257110	Neuropeptide Y ₂	92821	hum	2	10 μM	4								
258590	Nicotinic Acetylcholine	92737	hum	2	10 μM	5								
260110	Opiate δ (OP1, DOP)	92824	hum	2	10 μM	-12								
260210	Opiate κ (OP2, KOP)	92823	hum	2	10 μM	6								
260410	Opiate μ (OP3, MOP)	92822	hum	2	10 μM	-8								
264500	Phorbol Ester	92834	mous	2	10 μM	3								
265010	Platelet Activating Factor (PAF)	92835	hum	2	10 μM	3								
265600	Potassium Channel [K _{ATP}]	92637	syh	2	10 μM	9								
268700	Purinergic P _{2X}	92638	rabbi	2	10 μM	-1								
268810	Purinergic P _{2Y}	92649	rat	2	10 μM	-1								
271110	Serotonin (5-Hydroxytryptamine) 5-HT _{1A}	92716	hum	2	10 μM	-1								
271910	Serotonin (5-Hydroxytryptamine) 5-HT ₃	92629	hum	2	10 μM	-1								
278110	Sigma σ ₁	92925	hum	2	10 μM	16								
278200	Sigma σ ₂	92926	rat	2	10 μM	1								
279450	Sodium Channel, Site 1	92838	rat	2	10 μM	0								
279510	Sodium Channel, Site 2	92619	rat	2	10 μM	5								

*Batch: Represents compounds tested concurrently in the same assay(s).

†Results with ≥ 50% stimulation or inhibition are boldfaced. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

gp=guinea pig; hum=human; syh=syrian hamster

Figure 34

CAT. #	TARGET	BATCH*	SPP.	n=	CONC.	% INHIBITION						IC ₅₀	K _i	n _H	R
						%	↓	↓	↓	↓	↓				
255510	Tachykinin NK ₁	92831	hum	2	10 µM	-10									
285010	Testosterone	93005	rat	2	10 µM	8									
220320	Transporter, Dopamine (DAT)	92605	hum	2	10 µM	9									
226400	Transporter, GABA	92827	rat	2	10 µM	0									
204410	Transporter, Norepinephrine (NET)	92606	hum	2	10 µM	86									
◆		93798	hum	2	30 µM	97						0.203 µM	0.201 µM	0.733	
◆				2	10 µM	94									
◆				2	3 µM	90									
◆				2	1 µM	77									
◆				2	0.3 µM	55									
◆				2	0.1 µM	39									
◆		94109	hum	2	3 µM	84						0.237 µM	0.235 µM	0.706	
◆				2	1 µM	73									
◆				2	0.3 µM	55									
				2	0.1 µM	37									
				2	0.03 µM	16									
◆		94317	hum	2	3 µM	86						0.22 µM	0.218 µM	0.596	
◆				2	1 µM	71									
◆				2	0.3 µM	51									
				2	0.1 µM	38									
				2	0.03 µM	26									
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	92602	hum	2	10 µM	99									
◆		93802	hum	2	1 µM	96						0.0139 µM	7.4 nM	0.704	
◆				2	0.3 µM	87									
◆				2	0.1 µM	85									
◆				2	0.03 µM	63									
				2	10 nM	38									
				2	3 nM	30									
◆		94111	hum	2	0.1 µM	89						0.0111 µM	5.89 nM	0.864	
◆				2	0.03 µM	70									
				2	10 nM	48									
				2	3 nM	21									
				2	1 nM	17									

*Batch: Represents compounds tested concurrently in the same assay(s).

◆ Denotes item meeting criteria for significance

†Results with ≥ 50% stimulation or inhibition are boldfaced. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

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Figure 35

CAT. #	TARGET	BATCH*	SPP.	n=	CONC.	% INHIBITION					IC ₅₀	K _i	n _H	R
						-100	-50	0	50	100				
						%	↓	↓	↓	↓	↓			
◆ 274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	94318	hum	2	0.1 μM	88						0.013 μM	6.91 nM	0.906
				2	0.03 μM	69								
				2	10 nM	42								
				2	3 nM	18								
				2	1 nM	15								

*Batch: Represents compounds tested concurrently in the same assay(s).

◆ Denotes item meeting criteria for significance

†Results with ≥ 50% stimulation or inhibition are boldfaced. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

gp=guinea pig; hum=human; syh=syrian hamster

Figure 36

CAT. #	ASSAY NAME	REFERENCE COMPOUND	HISTORICAL			CONCURRENT MIC	
			IC ₅₀	K _i	n _H	BATCH*	IC ₅₀
118050	CYP450, 1A2	Furafylline	0.96 µM			93172	0.835 µM
118070	CYP450, 2C19	Tranylcypromine	8.1 µM			93174	8.68 µM
118060	CYP450, 2C9	Sulfaphenazole	0.77 µM			93173	0.453 µM
118080	CYP450, 2D6	Quinidine	0.057 µM			93175	0.0368 µM
118090	CYP450, 3A4	Ketoconazole	0.22 µM			92943	0.263 µM
200510	Adenosine A ₁	R(-)-PIA	0.44 µM	0.26 µM	0.8	92728	0.549 µM
200610	Adenosine A _{2A}	CGS-21680	0.46 µM	0.26 µM	0.9	92729	0.118 µM
203100	Adrenergic α _{1A}	Prazosin	0.69 nM	0.28 nM	0.9	92918	0.385 nM
203200	Adrenergic α _{1B}	Prazosin	0.27 nM	0.15 nM	1	92919	0.238 nM
203400	Adrenergic α _{1D}	Prazosin	0.88 nM	0.43 nM	0.7	92920	0.595 nM
203620	Adrenergic α _{2A}	Yohimbine	8.4 nM	3.1 nM	0.9	92621	3.35 nM
203710	Adrenergic α _{2B}	Yohimbine	0.014 µM	6.4 nM	1	92922	0.0341 µM
204010	Adrenergic β ₁	S(-)-Propranolol	2.5 nM	1.4 nM	0.8	92731	1.91 nM
204110	Adrenergic β ₂	S(-)-Propranolol	0.78 nM	0.54 nM	1.2	92732	0.448 nM
212500	Bradykinin B ₁	(Des-Arg ¹⁰)-Kallidin	1.6 nM	0.27 nM	0.9	92644	2 nM
212610	Bradykinin B ₂	Bradykinin	0.89 nM	0.53 nM	0.9	92828	0.897 nM
214510	Calcium Channel L-Type, Benzothiazepine	Diltiazem	0.036 µM	0.032 µM	0.9	92613	0.0337 µM
214600	Calcium Channel L-Type, Dihydropyridine	Nitrendipine	0.72 nM	0.46 nM	0.9	92614	1.31 nM
216000	Calcium Channel N-Type	ω-Conotoxin GVIA	0.034 nM	0.028 nM	1.6	92708	0.0117 nM
219500	Dopamine D ₁	R(+)-SCH-23390	1.4 nM	0.7 nM	0.9	92810	1.48 nM
219600	Dopamine D _{2L}	Spiperone	0.58 nM	0.19 nM	1.2	92811	0.356 nM
219800	Dopamine D ₃	Spiperone	0.36 nM	0.12 nM	0.9	92813	0.73 nM
219900	Dopamine D _{4L}	Spiperone	0.98 nM	0.34 nM	1	92814	1.87 nM
224010	Endothelin ET _A	Endothelin-1	0.23 nM	0.14 nM	1.1	92735	0.327 nM
224110	Endothelin ET _B	Endothelin-1	0.13 nM	0.06 nM	0.9	92736	0.0785 nM
225500	Epidermal Growth Factor (EGF)	Epidermal Growth Factor (EGF) (human)	0.39 nM	0.15 nM	1.2	92641	0.169 nM
226010	Estrogen ERα	Diethylstilbestrol	1.1 nM	0.31 nM	1.1	92633	0.52 nM
226500	GABA _A , Agonist Site	GABA	0.08 µM	0.063 µM	0.8	92616	0.0641 µM
226600	GABA _A , Benzodiazepine, Central	Diazepam	0.016 µM	0.013 µM	0.8	92830	0.011 µM
228510	GABA _B , Non-Selective	CGP-54626	1.8 nM	1.4 nM	1	92715	1.96 nM
232010	Glucocorticoid	Dexamethasone	0.041 µM	0.019 µM	0.9	92894	9.03 nM
232700	Glutamate, Kainate	L-Glutamate	0.24 µM	0.17 µM	0.8	92635	0.272 µM
232810	Glutamate, NMDA, Agonism	L-Glutamate	0.41 µM	0.37 µM	0.9	92720	0.303 µM
232910	Glutamate, NMDA, Glycine	MDL-105519	0.022 µM	0.021 µM	0.6	92912	5.28 nM
233000	Glutamate, NMDA, Phencyclidine	Dizolcipine (MK-801)	5.1 nM	3.4 nM	0.7	92636	5.42 nM

*Batch: Represents compounds tested concurrently in the same assay(s).

Figure 37

CAT. #	ASSAY NAME	REFERENCE COMPOUND	HISTORICAL			CONCURRENT MIC	
			IC ₅₀	K _i	n _H	BATCH*	IC ₅₀
239610	Histamine H ₁	Pyrilamine	3.3 nM	1.6 nM	1	92617	3.32 nM
239710	Histamine H ₂	Tiotidine	0.022 µM	0.018 µM	1.1	92618	0.028 µM
239810	Histamine H ₃	R(-)-α-Methylhistamine (RAMH)	5.2 nM	2.3 nM	0.9	92853	4.6 nM
241000	Imidazoline I ₂ , Central	Idazoxan	0.012 µM	8 nM	1	92836	6.93 nM
243510	Interleukin IL-1, Non-Selective	Interleukin-1α (IL-1α)	0.027 nM	10 pM	1	92929	0.0417 nM
250600	Leukotriene LTD ₄	Leukotriene D ₄ (LTD ₄)	1.4 nM	0.7 nM	1	92643	0.731 nM
252600	Muscarinic M ₁	4-DAMP	4.3 nM	1 nM	1	92840	3.82 nM
252700	Muscarinic M ₂	4-DAMP	0.013 µM	4.6 nM	0.9	92841	0.0219 µM
252800	Muscarinic M ₃	4-DAMP	3.9 nM	0.83 nM	1	92842	3.21 nM
257000	Neuropeptide Y ₁	Neuropeptide Y (human, rat)	4 nM	3.9 nM	1	92820	1.06 nM
257110	Neuropeptide Y ₂	Neuropeptide Y (13-36) (porcine)	4.4 nM	2.4 nM	0.7	92821	2.28 nM
258590	Nicotinic Acetylcholine	(+)-Epibatidine	0.071 nM	0.049 µM	0.9	92737	0.0545 nM
260110	Opiate δ (OP1, DOP)	Naltrindole	0.92 nM	0.32 nM	1	92824	0.85 nM
260210	Opiate κ (OP2, KOP)	U-69593	0.016 µM	6.4 nM	0.5	92823	7.68 nM
260410	Opiate μ (OP3, MOP)	DAMGO	0.02 µM	8.1 nM	0.6	92822	0.011 µM
264500	Phorbol Ester	PMA	9.1 nM	6.8 nM	1.1	92834	9.95 nM
265010	Platelet Activating Factor (PAF)	PAF	0.28 nM	0.15 nM	0.9	92835	0.548 nM
265600	Potassium Channel [K _{ATP}]	Glyburide	0.018 µM	2 nM	0.8	92637	8.04 nM
268700	Purinergic P _{2X}	α, β-Methylene ATP	0.082 µM	0.018 µM	1.1	92638	0.0764 µM
268810	Purinergic P _{2Y}	ATP	0.018 µM	0.018 µM	0.9	92649	0.038 µM
271110	Serotonin (5-Hydroxytryptamine) 5-HT _{1A}	Metergoline	4.1 nM	2.3 nM	0.9	92716	6.6 nM
271910	Serotonin (5-Hydroxytryptamine) 5-HT ₃	MDL-72222	0.011 µM	2.5 nM	0.8	92629	0.0157 µM
278110	Sigma σ ₁	Haloperidol	0.021 µM	8.8 nM	0.9	92925	7.67 nM
278200	Sigma σ ₂	Ifenprodil	8 nM	4.9 nM	0.7	92926	3.55 nM
279450	Sodium Channel, Site 1	Saxitoxin	1.7 nM	0.7 nM	1	92838	2.31 nM
279510	Sodium Channel, Site 2	Dibucaine	0.61 µM	0.55 µM	0.9	92619	0.892 µM
255510	Tachykinin NK ₁	L-703,606	0.025 µM	0.014 µM	0.8	92831	0.0217 µM
285010	Testosterone	Testosterone	6.5 nM	4.3 nM	1	93005	6.37 nM
220320	Transporter, Dopamine (DAT)	GBR-12909	1.7 nM	1.3 nM	0.9	92605	0.692 nM
226400	Transporter, GABA	NO-711	0.2 µM	0.2 µM	1.1	92827	0.214 µM
204410	Transporter, Norepinephrine (NET)	Desipramine	0.93 nM	0.92 nM	0.6	92606	0.83 nM
		Desipramine	0.93 nM	0.92 nM	0.6	93798	2.06 nM

*Batch: Represents compounds tested concurrently in the same assay(s).

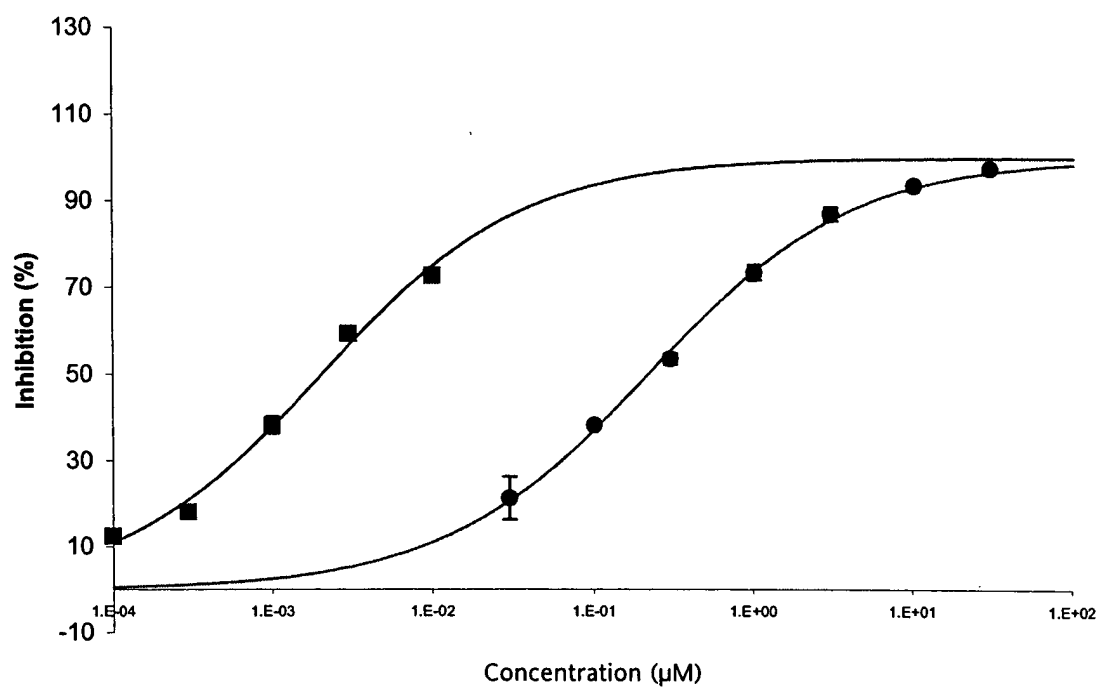
-133-

Figure 38

CAT. #	ASSAY NAME	REFERENCE COMPOUND	HISTORICAL			CONCURRENT MIC	
			IC ₅₀	K _I	n _H	BATCH*	IC ₅₀
204410	Transporter, Norepinephrine (NET)	Desipramine	0.93 nM	0.92 nM	0.6	94109	2.13 nM
		Desipramine	0.93 nM	0.92 nM	0.6	94317	1.96 nM
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	GBR-12909	0.11 µM	0.057 µM	0.8	92602	0.0667 µM
		GBR-12909	0.11 µM	0.057 µM	0.8	93802	0.0941 µM
		GBR-12909	0.11 µM	0.057 µM	0.8	94111	0.0671 µM
		GBR-12909	0.11 µM	0.057 µM	0.8	94318	0.103 µM

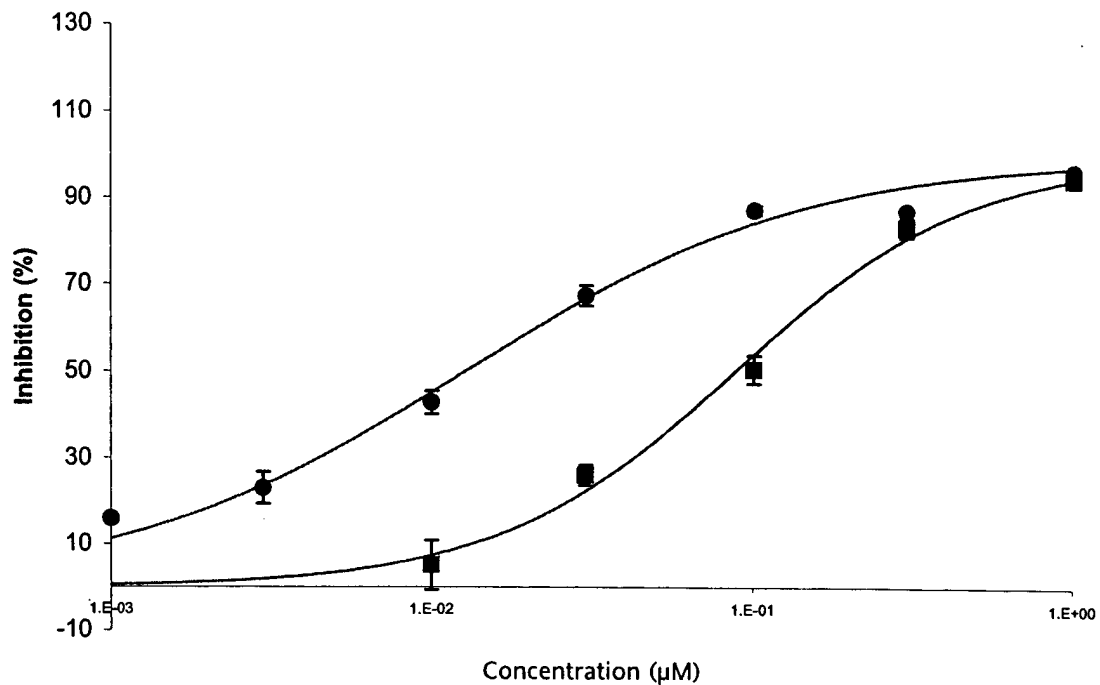
*Batch: Represents compounds tested concurrently in the same assay(s).

Figure 39



Compound	IC_{50}	K_i	n_H
Vial #1 (1036183)	$0.22 \pm 0.01 \mu M$	$0.218 \pm 0.01 \mu M$	0.678 ± 0.042
■ Desipramine	$2.05 \pm 0.049 nM$	$2.03 \pm 0.048 nM$	0.694 ± 0.036

Figure 40



Compound	IC ₅₀	K _i	n _H
Vial #1 (1036183)	0.0127 ± 0.001 μ M	6.73 ± 0.442 nM	0.825 ± 0.0616
■ GBR-12909	0.088 ± 0.0107 μ M	0.0467 ± 0.006 μ M	1.17 ± 0.088

Figure 41

COMPOUND CODE	PT NUMBER	BATCH*	SPP.	n=	CONC.	†% INHIBITION					IC ₅₀	K _i	n _H	R
						%	-100	-50	0	50	100			
212610	Bradykinin B ₂													
	Vial # 2	1037044	94766	hum	2	10 µM	-15							
	Vial # 3	1037045	94766	hum	2	10 µM	-2							
118090	CYP450, 3A4													
	Vial # 2	1037044	95160	hum	2	10 µM	24							
	Vial # 3	1037045	95160	hum	2	10 µM	39							
214510	Calcium Channel L-Type, Benzothiazepine													
	Vial # 2	1037044	94767	rat	2	10 µM	26							
	Vial # 3	1037045	94767	rat	2	10 µM	34							
204410	Transporter, Norepinephrine (NET)													
♦	Vial # 2	1037044	94760	hum	2	10 µM	92							
♦			95109	hum	2	3 µM	85				0.0978 µM	0.097 µM	0.62	
♦				2	1 µM	82								
♦				2	0.3 µM	63								
♦				2	0.1 µM	59								
♦				2	0.03 µM	30								
				2	10 nM	16								
♦			95324	hum	2	3 µM	86				0.101 µM	0.1 µM	0.493	
♦				2	1 µM	74								
♦				2	0.3 µM	63								
♦				2	0.1 µM	51								
				2	0.03 µM	35								
♦			95371	hum	2	3 µM	84				0.138 µM	0.136 µM	0.64	
♦				2	1 µM	77								
♦				2	0.3 µM	66								
				2	0.1 µM	47								
				2	0.03 µM	23								
♦	Vial # 3	1037045	94760	hum	2	10 µM	84							
♦			94891	hum	2	30 µM	87				1.67 µM	1.65 µM	0.745	
♦				2	10 µM	78								

* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.

♦ Denotes item meeting criteria for significance

† Results with ≥ 50% stimulation or inhibition are highlighted. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

hum=human

Figure 42

COMPOUND CODE	PT NUMBER	BATCH*	SPP.	n=	CONC.	†% INHIBITION					IC ₅₀	K _I	n _H	R	
						%	-100 ↓	-50 ↓	0 ↓	50 ↓					100 ↓
204410 Transporter, Norepinephrine (NET)															
♦	Vial # 3	1037045	94891	hum	2	3 μM	61						1.67 μM	1.65 μM	0.745
					2	1 μM	46								
					2	0.3 μM	18								
					2	0.1 μM	9								
♦			95109	hum	2	30 μM	93						1.43 μM	1.42 μM	0.77
♦					2	10 μM	77								
♦					2	3 μM	66								
					2	1 μM	45								
					2	0.3 μM	21								
♦			95324	hum	2	30 μM	78						1.95 μM	1.93 μM	0.523
♦					2	10 μM	72								
♦					2	3 μM	57								
					2	1 μM	40								
					2	0.3 μM	27								
274020 Transporter, Serotonin (5-Hydroxytryptamine) (SERT)															
♦	Vial # 2	1037044	94762	hum	2	10 μM	98								
♦			95110	hum	2	0.3 μM	95						7.17 nM	3.81 nM	0.999
♦					2	0.1 μM	93								
♦					2	0.03 μM	80								
♦					2	10 nM	59								
					2	3 nM	31								
					2	1 nM	10								
♦			95326	hum	2	0.1 μM	88						8.68 nM	4.61 nM	0.906
♦					2	0.03 μM	77								
♦					2	10 nM	53								
					2	3 nM	28								
					2	1 nM	11								
♦			95372	hum	2	0.1 μM	92						6.03 nM	3.2 nM	0.942
♦					2	0.03 μM	82								
♦					2	10 nM	62								

* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.

♦ Denotes item meeting criteria for significance

† Results with ≥ 50% stimulation or inhibition are highlighted. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

hum=human

Figure 43

COMPOUND CODE	PT NUMBER	BATCH*	SPP.	n=	CONC.	†% INHIBITION					IC ₅₀	K _I	n _H	R	
						%	-100	-50	0	50					100
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)														
	Vial # 2	1037044	95372	hum	2	3 nM	35						6.03 nM	3.2 nM	0.942
					2	1 nM	14								
◆	Vial # 3	1037045	94762	hum	2	10 µM	100								
◆			95110	hum	2	1 µM	96						0.014 µM	7.45 nM	0.907
◆					2	0.3 µM	93								
◆					2	0.1 µM	84								
◆					2	0.03 µM	67								
					2	10 nM	44								
					2	3 nM	17								
◆			95326	hum	2	0.3 µM	91						0.0197 µM	0.0105 µM	0.869
◆					2	0.1 µM	81								
◆					2	0.03 µM	59								
					2	10 nM	36								
					2	3 nM	16								
◆			95372	hum	2	0.3 µM	97						0.0123 µM	6.52 nM	1.05
◆					2	0.1 µM	89								
◆					2	0.03 µM	72								
					2	10 nM	45								
					2	3 nM	18								

* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.

♦ Denotes item meeting criteria for significance

† Results with ≥ 50% stimulation or inhibition are highlighted. (Negative values correspond to stimulation of binding or enzyme activity)

R=Additional Comments

hum=human

Figure 44

CELLULAR ASSAYS							%RESPONSE			
COMPOUND CODE	PT NUMBER	BATCH*	TISSUE, SPECIES	n=	CONC.	CRITERIA RESP.	AG.	ANT.	R	
302100 Cytotoxicity, Norepinephrine Uptake										
Vial #1	1036183	95055	MDCK cells, hum	2	10 µM	≥ ± 50%			9	
Vial #1	1036183	95055	MDCK cells, hum	2	1 µM	≥ ± 50%			8	
			MDCK cells, hum	2	0.1 µM	≥ ± 50%			-4	
			MDCK cells, hum	2	10 nM	≥ ± 50%			0	
			MDCK cells, hum	2	1 nM	≥ ± 50%			-8	
Vial # 2	1037044	95055	MDCK cells, hum	2	10 µM	≥ ± 50%			11	
			MDCK cells, hum	2	1 µM	≥ ± 50%			14	
			MDCK cells, hum	2	0.1 µM	≥ ± 50%			7	
			MDCK cells, hum	2	10 nM	≥ ± 50%			9	
			MDCK cells, hum	2	1 nM	≥ ± 50%			0	
Vial # 3	1037045	95055	MDCK cells, hum	2	10 µM	≥ ± 50%			-6	
			MDCK cells, hum	2	1 µM	≥ ± 50%			-1	
			MDCK cells, hum	2	0.1 µM	≥ ± 50%			-6	
			MDCK cells, hum	2	10 nM	≥ ± 50%			-6	
			MDCK cells, hum	2	1 nM	≥ ± 50%			-3	
364100 Cytotoxicity, Serotonin (5-Hydroxytryptamine) Uptake										
Vial #1	1036183	95056	HEK-293 cells, hum	2	10 µM	≥ ± 50%			2	
			HEK-293 cells, hum	2	1 µM	≥ ± 50%			-7	
			HEK-293 cells, hum	2	0.1 µM	≥ ± 50%			0	
			HEK-293 cells, hum	2	10 nM	≥ ± 50%			-2	
			HEK-293 cells, hum	2	1 nM	≥ ± 50%			-3	
Vial # 2	1037044	95056	HEK-293 cells, hum	2	10 µM	≥ ± 50%			-8	
			HEK-293 cells, hum	2	1 µM	≥ ± 50%			-7	
			HEK-293 cells, hum	2	0.1 µM	≥ ± 50%			-2	
			HEK-293 cells, hum	2	10 nM	≥ ± 50%			0	
			HEK-293 cells, hum	2	1 nM	≥ ± 50%			2	
Vial # 3	1037045	95056	HEK-293 cells, hum	2	10 µM	≥ ± 50%			-3	
			HEK-293 cells, hum	2	1 µM	≥ ± 50%			-6	
			HEK-293 cells, hum	2	0.1 µM	≥ ± 50%			-6	

* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.

♦ Denotes item meeting criteria for significance

Ag.=Agonist; Ant.=Antagonist; Resp.=Response; ND=Assay Test Not Done; R=Additional Comments

hum=human

Figure 45

CELLULAR ASSAYS							%RESPONSE		
COMPOUND CODE	PT NUMBER	BATCH*	TISSUE, SPECIES	n=	CONC.	CRITERIA RESP.	AG.	ANT.	R
364100 Cytotoxicity, Serotonin (5-Hydroxytryptamine) Uptake									
Vial # 3	1037045	95056	HEK-293 cells, hum	2	10 nM	≥ ± 50%			-4
			HEK-293 cells, hum	2	1 nM	≥ ± 50%			-1
302000 Uptake, Norepinephrine									
♦ Vial #1	1036183	94864	MDCK cells, hum	2	10 µM	≥ ± 50%			95
♦			MDCK cells, hum	2	1 µM	≥ ± 50%			95
♦			MDCK cells, hum	2	0.1 µM	≥ ± 50%			78
			MDCK cells, hum	2	10 nM	≥ ± 50%			25
			MDCK cells, hum	2	1 nM	≥ ± 50%			7
♦ Vial # 2	1037044	94864	MDCK cells, hum	2	10 µM	≥ ± 50%			99
♦			MDCK cells, hum	2	1 µM	≥ ± 50%			98
♦			MDCK cells, hum	2	0.1 µM	≥ ± 50%			90
♦			MDCK cells, hum	2	10 nM	≥ ± 50%			50
			MDCK cells, hum	2	1 nM	≥ ± 50%			5
♦ Vial # 3	1037045	94864	MDCK cells, hum	2	10 µM	≥ ± 50%			97
♦			MDCK cells, hum	2	1 µM	≥ ± 50%			83
			MDCK cells, hum	2	0.1 µM	≥ ± 50%			48
			MDCK cells, hum	2	10 nM	≥ ± 50%			20
			MDCK cells, hum	2	1 nM	≥ ± 50%			15
364000 Uptake, Serotonin (5-Hydroxytryptamine)									
♦ Vial #1	1036183	94865	HEK-293 cells, hum	2	10 µM	≥ ± 50%			100
♦			HEK-293 cells, hum	2	1 µM	≥ ± 50%			94
♦			HEK-293 cells, hum	2	0.1 µM	≥ ± 50%			75
			HEK-293 cells, hum	2	10 nM	≥ ± 50%			38
			HEK-293 cells, hum	2	1 nM	≥ ± 50%			4
♦ Vial # 2	1037044	94865	HEK-293 cells, hum	2	10 µM	≥ ± 50%			99
♦			HEK-293 cells, hum	2	1 µM	≥ ± 50%			96
♦			HEK-293 cells, hum	2	0.1 µM	≥ ± 50%			80
			HEK-293 cells, hum	2	10 nM	≥ ± 50%			33
			HEK-293 cells, hum	2	1 nM	≥ ± 50%			5

* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.

♦ Denotes item meeting criteria for significance

Ag.=Agonist; Ant.=Antagonist; Resp.=Response; ND=Assay Test Not Done; R=Additional Comments

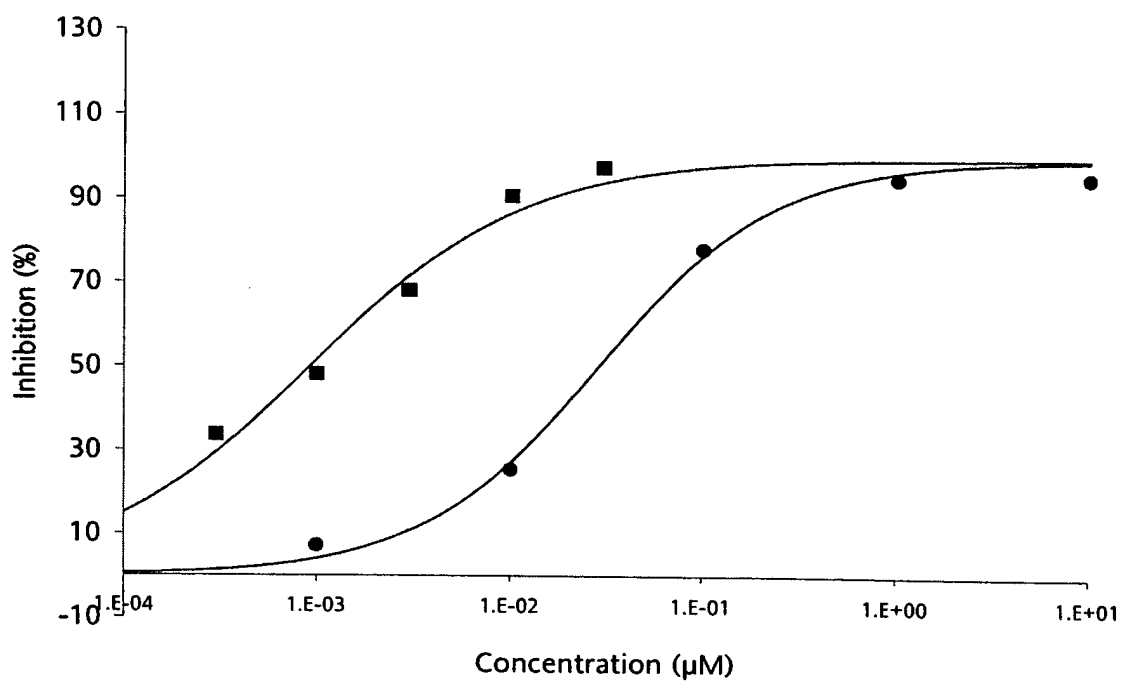
hum=human

Figure 46

CELLULAR ASSAYS						%RESPONSE			
COMPOUND CODE	PT NUMBER	BATCH*	TISSUE, SPECIES	n=	CONC.	CRITERIA	RESP.	AG.	ANT. R
364000 Uptake, Serotonin (5-Hydroxytryptamine)									
♦ Vial # 3	1037045	94865	HEK-293 cells, hum	2	10 µM	≥ ± 50%			100
♦			HEK-293 cells, hum	2	1 µM	≥ ± 50%			88
♦			HEK-293 cells, hum	2	0.1 µM	≥ ± 50%			65
			HEK-293 cells, hum	2	10 nM	≥ ± 50%			33
			HEK-293 cells, hum	2	1 nM	≥ ± 50%			-4

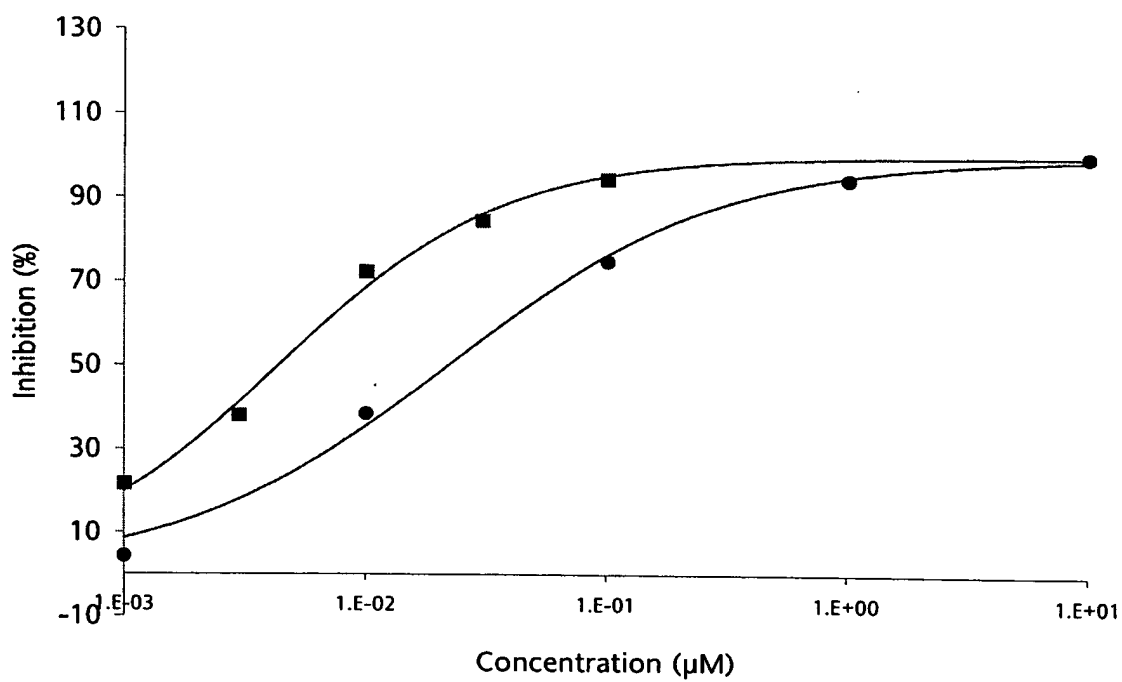
* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.
 ♦ Denotes item meeting criteria for significance
 Ag.=Agonist; Ant.=Antagonist; Resp.=Response; ND=Assay Test Not Done; R=Additional Comments
 hum=human

Figure 47



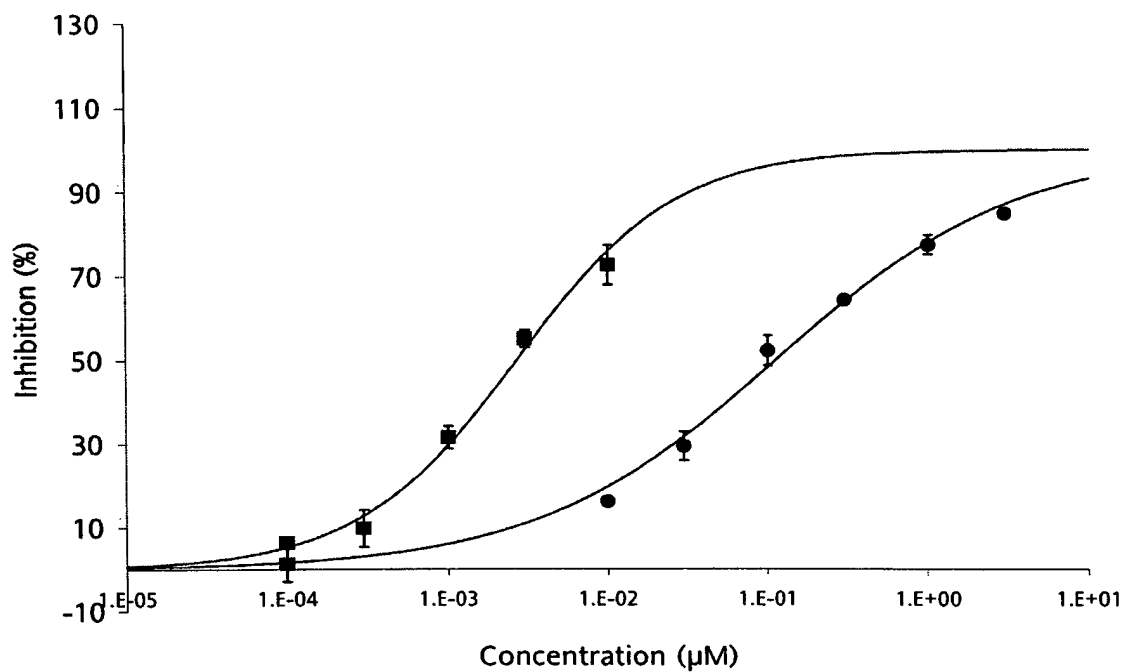
Compound	IC ₅₀	n _H
CEL - 1 (1036183)	0.0286 μM	0.94
■ Desipramine	0.922 nM	0.78

Figure 48



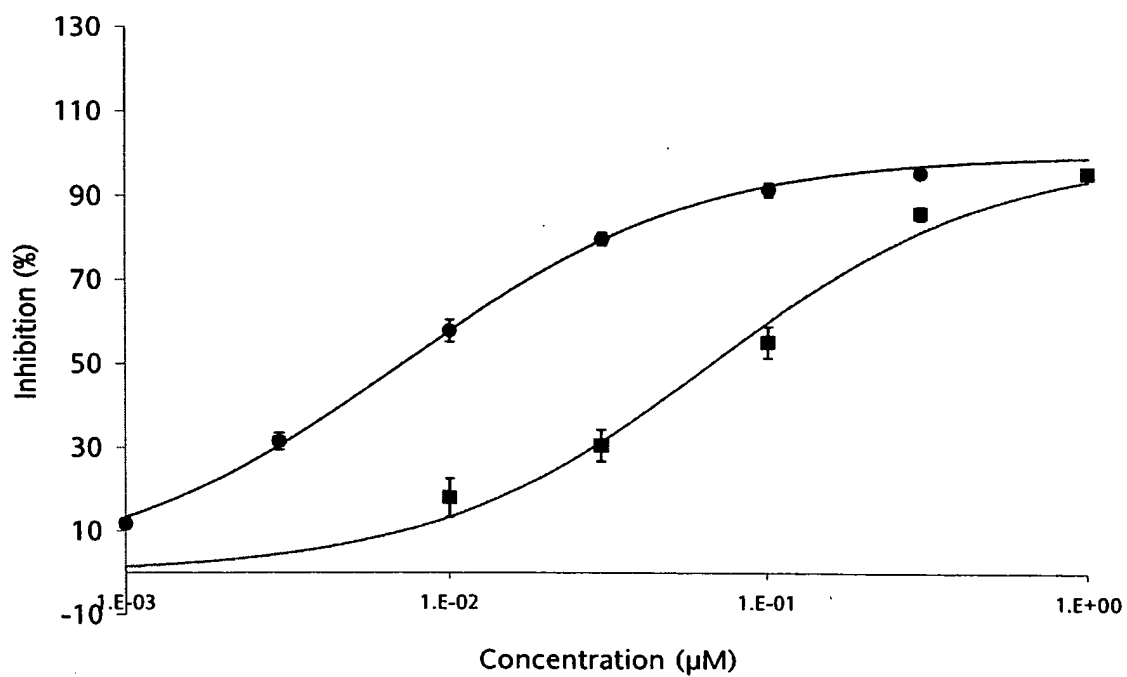
Compound	IC_{50}	n_H
CEL - 1 (1036183)	0.0217 μM	0.766
■ Fluoxetine	4.36 nM	0.943

Figure 49



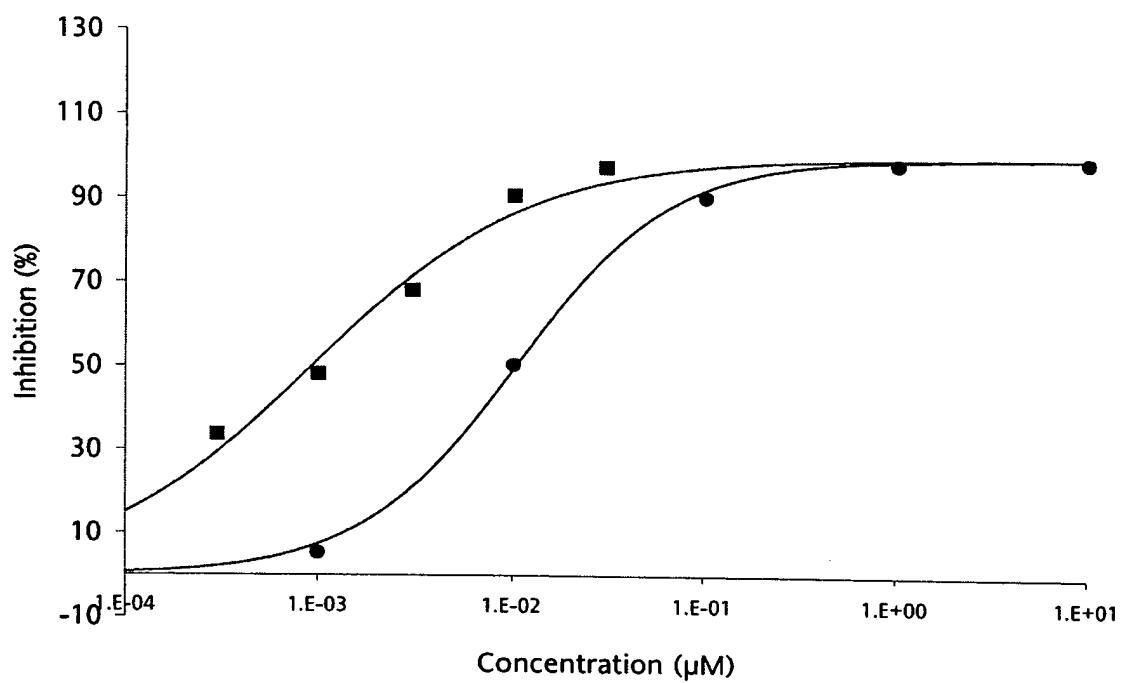
Compound	IC ₅₀	K _i	n _H
CEL - 3 (1037044)	0.112 ± 0.013 μM	0.111 ± 0.013 μM	0.584 ± 0.046
■ Desipramine	2.78 ± 0.498 nM	2.76 ± 0.494 nM	0.872 ± 0.008

Figure 50



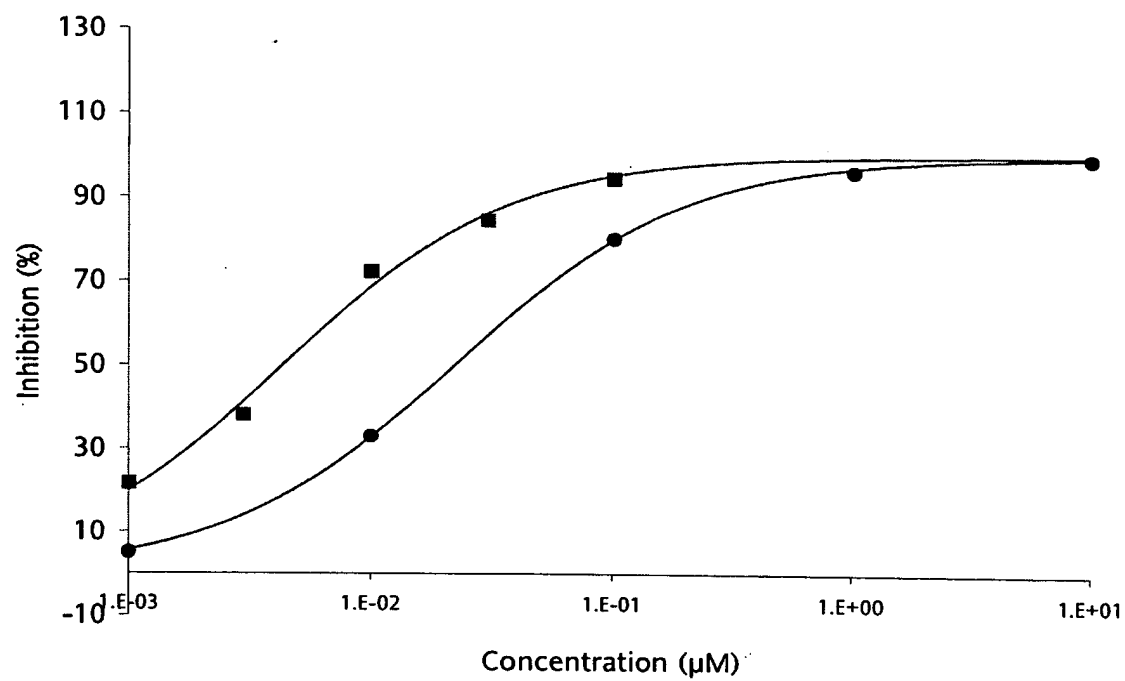
Compound	IC ₅₀	K _i	n _H
● CEL - 3 (1037044)	7.3 ± 0.768 nM	3.88 ± 0.408 nM	0.949 ± 0.027
■ GBR-12909	0.0675 ± 0.0105 μM	0.0359 ± 0.006 μM	1.01 ± 0.105

Figure 51



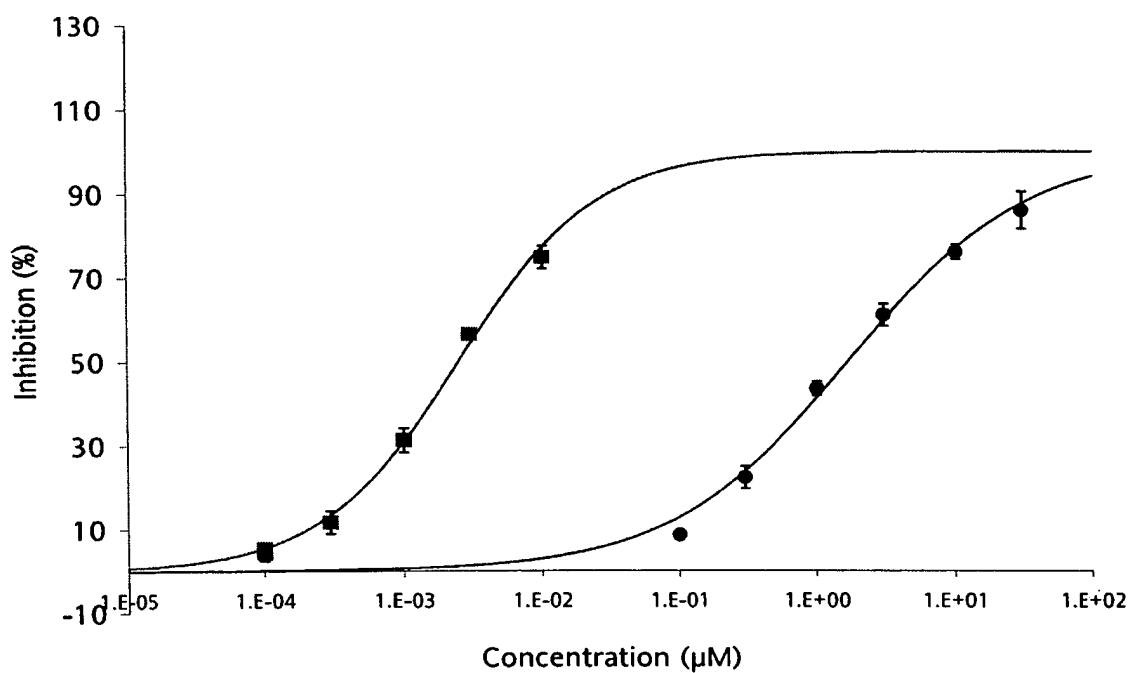
Compound	IC ₅₀	n _H
CEL - 3 (1037044)	0.0103 μM	1.08
■ Desipramine	0.922 nM	0.78

Figure 52



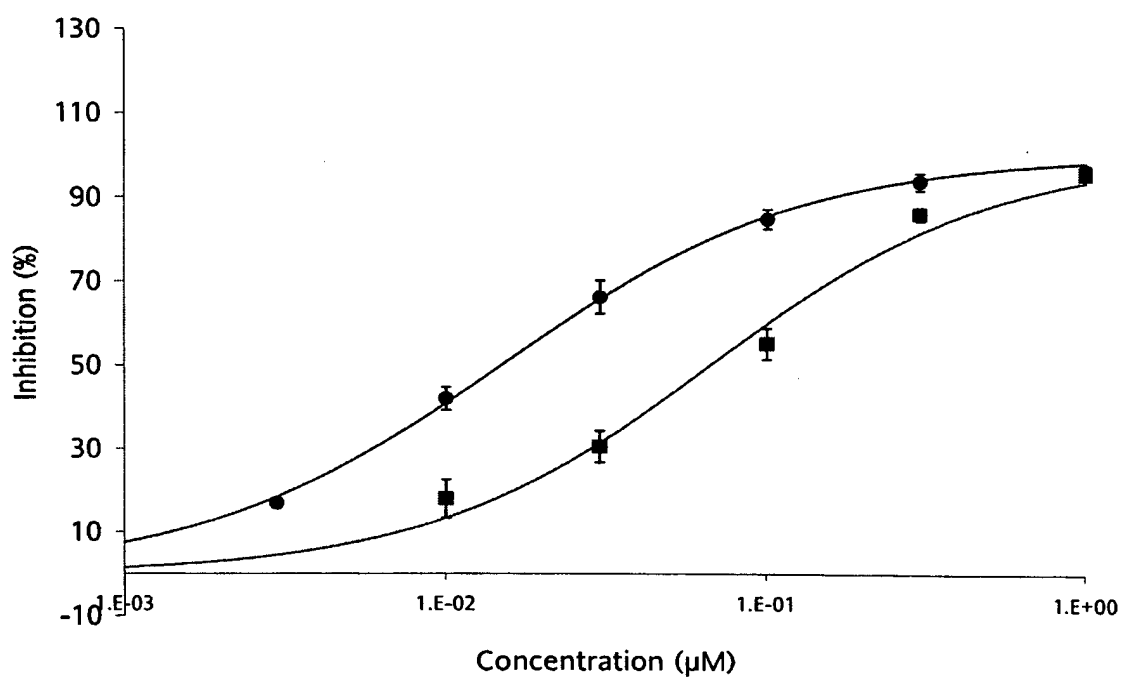
Compound	IC ₅₀	n _H
CEL - 3 (1037044)	0.022 μM	0.909
■ Fluoxetine	4.36 nM	0.943

Figure 53



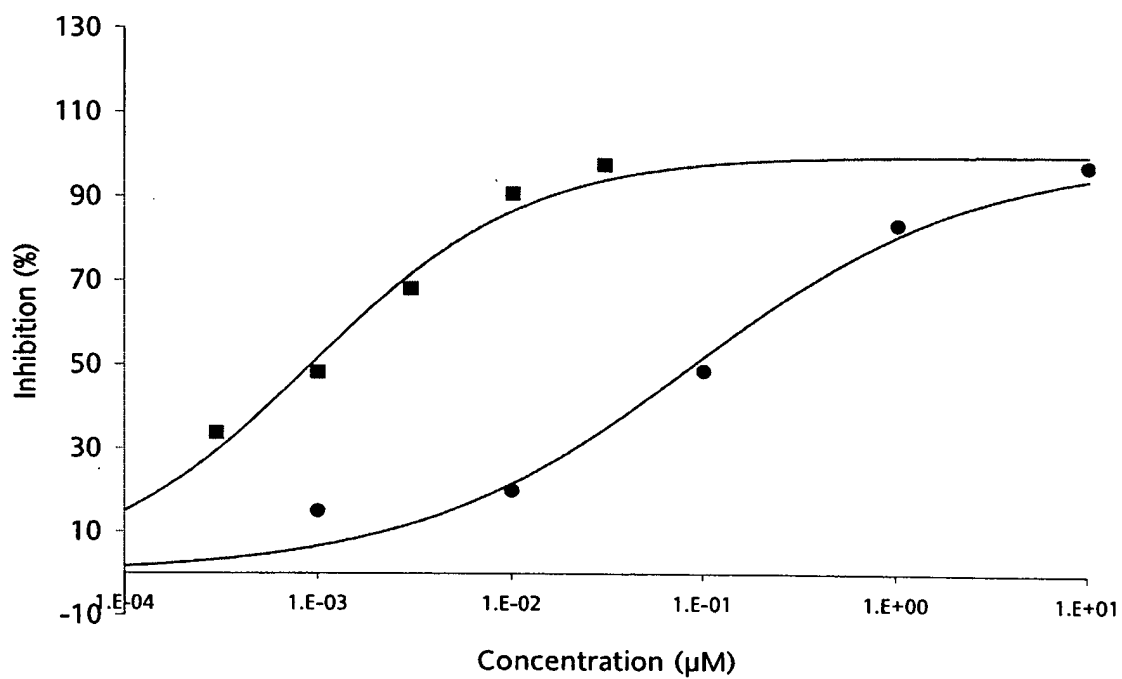
Compound	IC ₅₀	K _i	n _H
CEL - 5 (1037045)	1.68 ± 0.149 μM	1.67 ± 0.148 μM	0.679 ± 0.078
■ Desipramine	2.52 ± 0.292 nM	2.5 ± 0.289 nM	0.882 ± 0.016

Figure 54



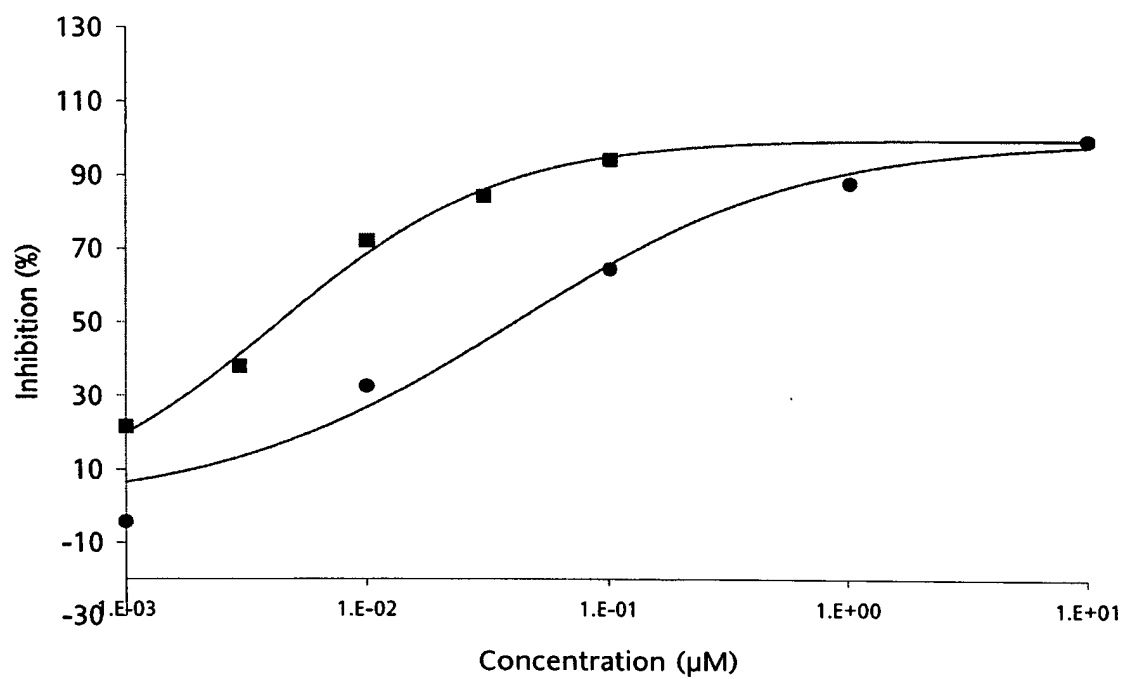
Compound	IC ₅₀	K _i	n _H
CEL - 5 (1037045)	0.0153 ± 0.002 μM	8.15 ± 1.19 nM	0.94 ± 0.054
■ GBR-12909	0.0675 ± 0.0105 μM	0.0359 ± 0.006 μM	1.01 ± 0.105

Figure 55



Compound	IC ₅₀	n _H
CEL - 5 (1037045)	0.0885 μ M	0.592
■ Desipramine	0.922 nM	0.78

Figure 56



Compound	IC ₅₀	n _H
CEL - 5 (1037045)	0.0403 μM	0.718
■ Fluoxetine	4.36 nM	0.943

Figure 57

CAT. #	ASSAY NAME	REFERENCE COMPOUND	HISTORICAL IC ₅₀ /EC ₅₀	CONCURRENT MIC	
				BATCH *	IC ₅₀ /EC ₅₀
302100	Cytotoxicity, Norepinephrine Uptake - Antagonist	DMSO	29 %	95055	19.9 %
364100	Cytotoxicity, Serotonin Uptake - Antagonist	DMSO	20 %	95056	27.5 %
302000	Uptake, Norepinephrine	Desipramine	1.9 nM	94864	0.922 nM
364000	Uptake, Serotonin	Fluoxetine	7.1 nM	94865	4.36 nM

* Batch: Represents compounds tested concurrently in the same assay(s).

‡ For some assays only a single concentration of reference compound is tested. Please refer to the individual response section (if applicable) of this report for the results.

Figure 58

CAT. #	ASSAY NAME	REFERENCE COMPOUND	HISTORICAL			CONCURRENT MIC	
			IC ₅₀	K _i	n _H	BATCH *	IC ₅₀
118090	CYP450, 3A4	Ketoconazole	0.22 µM			95160	0.355 µM
212610	Bradykinin B ₂	Bradykinin	0.89 nM	0.53 nM	0.9	94766	1.66 nM
214510	Calcium Channel L-Type, Benzothiazepine	Diltiazem	0.036 µM	0.032 µM	0.9	94767	0.0873 µM
204410	Transporter, Norepinephrine (NET)	Desipramine	0.93 nM	0.92 nM	0.6	94760	0.767 nM
		Desipramine	0.93 nM	0.92 nM	0.6	94891	2.89 nM
		Desipramine	0.93 nM	0.92 nM	0.6	95109	1.94 nM
		Desipramine	0.93 nM	0.92 nM	0.6	95324	2.73 nM
		Desipramine	0.93 nM	0.92 nM	0.6	95371	3.67 nM
274020	Transporter, Serotonin (5- Hydroxytryptamine) (SERT)	GBR-12909	0.11 µM	0.057 µM	0.8	94762	0.0707 µM
		GBR-12909	0.11 µM	0.057 µM	0.8	95110	0.0871 µM
		GBR-12909	0.11 µM	0.057 µM	0.8	95326	0.0644 µM
		GBR-12909	0.11 µM	0.057 µM	0.8	95372	0.0512 µM

* Batch: Represents compounds tested concurrently in the same assay(s). ‡ Partially soluble in *in vitro* test solvent.

Figure 59

<i>PRIMARY TESTS</i>							
CAT. #	PRIMARY BIOCHEMICAL ASSAY	SPECIES	CONC.	% INH.	IC ₅₀ *	K _i	n _H
204410	Transporter, Norepinephrine (NET)	hum	0.3 µM	51	0.22 ± 0.01 µM	0.218 ± 0.01 µM	0.678 ± 0.042
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	hum	0.03 µM	63	0.0127 ± 0.001 µM	6.73 ± 0.442 nM	0.825 ± 0.0616
<i>ABOVE PRIMARY TESTS IN RANK ORDER OF POTENCY</i>							
CAT. #	PRIMARY RADIOLIGAND ASSAY	SPECIES	CONC.	% INH.	IC ₅₀ *	K _i	n _H
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	hum	0.03 µM	63	0.0127 ± 0.001 µM	6.73 ± 0.442 nM	0.825 ± 0.0616
204410	Transporter, Norepinephrine (NET)	hum	0.3 µM	51	0.22 ± 0.01 µM	0.218 ± 0.01 µM	0.678 ± 0.042

*A standard error of the mean is presented where results are based on multiple, independent determinations.

gp=guinea pig; hum=human; syh=syrian hamster

Figure 60

PRIMARY TESTS								
PRIMARY BIOCHEMICAL ASSAY								
COMPOUND		PT NUMBER	SPECIES	CONC.	% INH.	IC ₅₀ *	K _i	n _H
204410	Transporter, Norepinephrine (NET)							
	Vial # 2	1037044	hum	0.1 μM	51	0.112 ± 0.013 μM	0.111 ± 0.0126	0.584 ± 0.046
	Vial # 3	1037045	hum	3 μM	57	1.68 ± 0.149 μM	1.67 ± 0.148 μM	0.679 ± 0.078
274020	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)							
	Vial # 2	1037044	hum	10 nM	53	7.3 ± 0.768 nM	3.88 ± 0.408 nM	0.949 ± 0.0269
	Vial # 3	1037045	hum	0.03 μM	59	0.0153 ± 0.002 μM	8.15 ± 1.19 nM	0.94 ± 0.054

‡ Partially soluble in *in vitro* test solvent.

* A standard error of the mean is presented where results are based on multiple, independent determinations.

hum=human

Figure 61

PRIMARY TESTS										
COMPOUND	PT NUMBER	PRIMARY CELLULAR ASSAY				% RESPONSE				
		SPECIES	CELL NAME	CONC.	CRITERIA	RESP.	AG.	ANT.	EC ₅₀ /IC ₅₀	*
302000 Uptake, Norepinephrine										
Vial #1	1036183	hum	MDCK cells	0.1 µM	≥ ± 50%			78	0.0286 µM	
Vial # 2	1037044	hum	MDCK cells	10 nM	≥ ± 50%			50	0.0103 µM	
Vial # 3	1037045	hum	MDCK cells	1 µM	≥ ± 50%			83	0.0885 µM	
364000 Uptake, Serotonin (5-Hydroxytryptamine)										
Vial #1	1036183	hum	HEK-293 cells	0.1 µM	≥ ± 50%			75	0.0217 µM	
Vial # 2	1037044	hum	HEK-293 cells	0.1 µM	≥ ± 50%			80	0.022 µM	
Vial # 3	1037045	hum	HEK-293 cells	0.1 µM	≥ ± 50%			65	0.0403 µM	

‡ Partially soluble in *in vitro* test solvent.

* A standard error of the mean is presented where results are based on multiple, independent determinations.

Ag.=Agonist; Ant.=Antagonist; Resp.=Response; ND=Assay Test Not Done

hum=human

Figure 62

SECONDARY CELLULAR ASSAY						% RESPONSE		
COMPOUND	PT NUMBER	SPECIES	CELL NAME	CONC.	CRITERIA	RESP.	AG	ANT. EC ₅₀ /IC ₅₀ *
Prim. Cat#: 302000	Sec. Cat#: 302100	Cytotoxicity, Norepinephrine Uptake						
Vial #1	1036183	hum	MDCK cells	10 µM	≥ ± 50%			9
Vial # 2	1037044	hum	MDCK cells	10 µM	≥ ± 50%			11
Vial # 3	1037045	hum	MDCK cells	10 µM	≥ ± 50%			-6
Prim. Cat#: 364000	Sec. Cat#: 364100	Cytotoxicity, Serotonin (5-Hydroxytryptamine) Uptake						
Vial #1	1036183	hum	HEK-293 cells	10 µM	≥ ± 50%			2
Vial # 2	1037044	hum	HEK-293 cells	10 µM	≥ ± 50%			-8
Vial # 3	1037045	hum	HEK-293 cells	10 µM	≥ ± 50%			-3

‡ Partially soluble in *in vitro* test solvent.

* A standard error of the mean is presented where results are based on multiple, independent determinations.

♦ Denotes item meeting criteria for significance

Ag.=Agonist; Ant.=Antagonist; Resp.=Response; ND=Assay Test Not Done
hum=human

Figure 63

Adverse Event	Frequency of Adverse Experiences (%)			
	Placebo N = 394	50 mg/day twice daily N = 426	100 mg/day twice daily N = 1871	200 mg/day twice daily N = 865
Nausea	10.9	12.7	11.2	19.4*
Headache	17.0	14.6	8.4	13.5
Increased Sweating	1.3	14.0	4.3*	11.6*
Constipation	4.3	8.0	6.5	11.4*
Insomnia	10.7	9.2	6.1	11.3
Dry mouth	5.6	9.4	7.9	9.0
Vomiting	3.6	3.8	3.9	7.9*
Abdominal Pain	5.1	6.1	6.5	7.6
Tremor	1.5	0.9	2.5	6.7*
Anxiety	1.3	2.8	4.1	5.1
Palpitations	1.8	2.3	2.7	4.6
Vertigo	1.8	1.6	5.0	4.5
Fatigue	3.0	2.8	2.5	4.4
Dysuria	0.3	1.4	2.1*	3.7*
Hot flushes	0	1.6	3.0	3.6
Somnolence	3.8	5.4	2.3	3.5
Agitation	3.0	1.6	3.3	2.9
Nervousness	2.0	4.2	2.0	2.8
Dyspepsia	4.1	3.5	2.1	2.2

* Significantly greater than placebo